New Medicine Recommendation
Aviptadil (VIP) 25micrograms / Phentolamine Mesilate 2mg (Invicorp) solution for injection

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

Recommendation: AMBER 0

Suitable for prescribing in primary care following recommendation or initiation by a specialist.

Reserved for patients not responding or intolerant to Alprostadil, as an option before referral for surgical procedure.

Little or no specific monitoring required.

Patient may need a regular review, but this would not exceed that required for other medicines routinely prescribed in primary care.

Brief prescribing document or information sheet may be required.

Primary care prescribers must be familiar with the drug to take on prescribing responsibility or must get the required information.

When recommending or handing over care, specialists should ask primary care prescribers to take over prescribing responsibility, and should give enough information about the indication, dose, monitoring requirements, use outside product licence and any necessary dose adjustments to allow them to confidently prescribe.

Summary of supporting evidence

- In one trial (Dinsmore 1999)[9] differential analysis of active drug vs placebo by underlying aetiology showed no statistical difference in efficacy of either 25micrograms VIP / 1mg phentolamine (VIP/P-1) or 25micrograms VIP / 2mg phentolamine (VIP/P-2).
- In the second trial (Sandhu 1999)[10] in the first section, 304 patients received treatment. Within this part of the trial, the effective dose was determined and non-responders were removed from progressing into the second section of the trial. The second section of the trial was divided into two consecutive parts (placebo controlled 1 and placebo controlled 2). Results from 172 patients of the 240 enrolled into placebo controlled 1 could be analysed, with 133 patients meeting full protocol completion criteria. Of the 133 patients completing placebo controlled 1, 126 participated in placebo controlled 2, with 105 completing the full protocol. Differential analysis of active drug vs placebo by underlying aetiology showed no statistical difference in efficacy of either VIP/P-1 or VIP/P-2. Within this trial were a subset of patients (183) who had previously withdrawn from one or more previous ED therapies. Of these 106 had previously been treated with alprostadil and a cumulative response rate of 59.4% and 81.1% was found when treating these patients with VIP/P-1 and VIP/P-2 respectively.
- In the third trial, VP007, (Shah 2007)[12] in the first section, 187 patients received treatment. Within this part of the trial, the effective dose was determined and non-responders were removed from progressing into the second section of the trial. Significantly fewer patients achieved a grade 3 erection after treatment with aviptadil/phentolamine than after treatment with alprostadil (137 [73%] and 155 [83%] respectively).
- Following section 2 of the VP007 trial (107 patients), the paper concludes that the

efficacy of aviptadil/phentolamine is similar to alprostadil. However, patients received a range of doses of aviptadil and phentolamine (12.5 or 25 micrograms and 0.5, 1.0 or 2.0 mg, respectively), either prepared from ampoules or administered in an auto-injector. Therefore not all patients received aviptadil/phentolamine as the licensed (25 micrograms/2 mg) dose and formulation. Similarly, patients received alprostadil at doses of 5–20 micrograms, and although the SPC states that the majority of patients achieve a satisfactory response within this dose range, doses of up to 60 micrograms can be used. It is unclear whether the doses used in VP 007 are fully representative of clinical practice for either medicine.

- In the small study conducted by Dinsmore (1998)[13] it was demonstrated that the combination of VIP and Phentolamine mesylate is an effective therapeutic option in patients unresponsive to conventional intracavernosal therapy.
- Within the trials, pain on injection was virtually absent, however, the auto-injector which is not currently licensed within the UK was mainly used within the trials, only VP007 included Invicorp in both ampoules and auto-injectors.
- Additional studies are needed to determine its efficacy and safety profile.

Details of Review

Name of medicine (generic & brand name): Aviptadil 25micrograms / Phentolamine Mesilate 2mg (Invicorp) [1]
Strengths and forms: 25micrograms / 2mg solution for injection, 0.35ml ampoule.
Dose and administration: Each ampoule (0.35ml) contains the correct amount for a single injection (the whole contents of the ampoule are to be injected). Injection frequency should not exceed once daily or three times weekly.
BNF therapeutic class / mode of action:[16] Chapter 7, Genito – urinary system, section 4.1 Erectile Dysfunction Phentolamine is a short acting alpha adrenoceptor antagonist that acts directly on vascular smooth muscle, resulting in vasodilatation and a decrease in blood pressure, as a result of the blockade of both post-junction vascular alpha 1 and alpha 2 adrenoceptors with almost the same effect. Phentolamine increases arterial inflow in the penis but has little effect on venous outflow. Aviptadil is a vasoactive intestinal polypeptide that acts as a smooth muscle relaxant causing venous occlusion in the corpus cavernosa. Therefore, in contrast to phentolamine, aviptadil reduces venous outflow in the penis.
Licensed indication(s): Invicorp is indicated for the symptomatic treatment of erectile dysfunction in adult males due to neurogenic, vasculogenic, psychogenic, or mixed aetiology.
Proposed use: Within licensed indication, reserved for patients not responding or intolerant to alprostadil, as an option before referral for surgical procedure.
Course and cost: Invicorp is supplied in boxes containing 2x 0.35ml glass ampoules with 2 syringes, 2 x 30G needles and 2 x 21G needles at £19.00 (£9.50 / injection, NHS list price) Invicorp is supplied in boxes containing 5x 0.35ml glass ampoules with 5 syringes, 5 x 30G needles and 5 x 21G needles at £47.50 (£9.50 / injection, NHS list price)
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). Initially 2.5 micrograms for 1 dose (first dose), followed by 5 micrograms for 1 dose (second

dose), to be given if some response to first dose, alternatively 7.5 micrograms for 1 dose (second dose), to be given if no response to first dose, then increased in steps of 5–10 micrograms, to obtain a dose suitable for producing erection lasting not more than 1 hour; if no response to dose then next higher dose can be given within 1 hour, if there is a response the next dose should not be given for at least 24 hours; usual dose 5–20 micrograms (max. per dose 60 micrograms), maximum frequency of injection not more than 3 times per week with at least 24 hour interval between injections.

Caverject NHS price / injection: 5 microgram = £7.73, 10 microgram = £9.24, 20 microgram = £11.94, 40 microgram = £21.58, Dual Chamber 10 microgram = £7.35, 20 microgram £9.50.

Relevant NICE guidance:

NICE – not yet reviewed

SMC – not yet reviewed

AWMSG – Advice No: 3216 – November 2016, currently not recommended for use (the clinical and cost effectiveness data presented in the submission were insufficient for AWMSG to recommend its use.) The company proposed the place in therapy of aviptadil/phentolamine as second-line, in patients with erectile dysfunction that does not respond to oral treatment with PDE5 inhibitors. The company had to show that aviptadil/phentolamine was more effective than alprostadil and did not focus on alprostadil failures. Currently in for resubmission – Reference No: 3435, AWMSG meeting date 21/06/2017.

Disease Background

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 (NHS Choices)

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.[2]

Several large epidemiological studies have shown a high prevalence and incidence of ED worldwide.

In the Massachusetts Male Aging Study (MMAS), the prevalence of ED was 52% in non-institutionalized 40 to 70-year-old men in the Boston area: 17.2%, 25.2% and 9.6% for minimal, moderate and complete ED, respectively.[2] The incidence of ED, calculated from longitudinal data in the MMAS, was 26 new cases per 1000 per year[3]. A large European study of men aged 30-80 reported a prevalence of 19%.[4] A UK study of men aged 18-75 showed a rate of 39% for lifetime ED with a current prevalence of 26%.[5] Both studies showed a steep age-related increase. These epidemiological studies provide different estimates of the prevalence of ED, which can be explained by the methodology design of the different surveys.

Approximately 25% of patients do not respond to phosphodiesterase type-5 inhibitors (PDE5 inhibitors).[6] Patients should be exposed to a minimum of 4 (preferably 8) of the highest tolerated dose of at least two drugs (taken sequentially, not concurrently) with adequate sexual stimulation. Patients should be followed up, ideally within 6 weeks of commencing therapy.

Intracavernous injection therapy is the most effective form of pharmacotherapy for ED and has been used for more than 20 years.[7] Providing the blood supply is good, an excellent result can be achieved in most men. It does not require an intact nerve supply and can therefore be highly effective after spinal cord injuries and after major pelvic surgery such as after radical prostatectomy. However, because of the invasive nature of the procedure it is not acceptable to some patients and their partners, and this may result in poor long-term compliance in those who do try it.[7,8] Compliance may be a particular problem if the

procedure is not explained clearly and fully at first consultation and if adequate support and follow-up visits are not provided.

Current treatment options

Alprostadil

NICE – injection not reviewed;
Erectile dysfunction: Alprostadil cream Evidence summary [ESNM50] Published date: December 2014

SMC – not reviewed

AWMSG – not reviewed

Alprostadil (Caverject, Viridal) was the first licensed drug approved for intracavernous ED treatment.

Alprostadil is normally used in doses from 5-40 µg. The erection occurs typically 5-15 minutes after penile injection and frequently last 30-40 minutes, although the duration can be dose dependent. Two or three visits are usually required to ascertain the correct dosage and teach the patient the technique. In patients with limited manual dexterity and in some other groups, the partner may be taught the technique.

Partner participation in the consultation and training programme can be valuable and improve long-term compliance. Some patients prefer to use an automatic injection pen that avoids a view of the needle and can help with the fear of penile puncture.

Efficacy and safety of alprostadil is summarised below:

- Efficacy rates are high – around 70-80% in the general ED population and higher in those without vascular disease
- Once properly taught the procedure has a high reproducibility and high satisfaction rate for both patients and their partners
- Long-term compliance rates however can be low with as many as 50% of patients stopping in the first 2-3 months[7,8]
- Careful counselling in the early stages with an easy availability of advice in the first few weeks can improve compliance
- Adverse effects of intracavernosal alprostadil include post-injection penile pain (in up to half patients after at least some of their injections)[7,8]
- Other complications include priapism (1%) and fibrosis (2%)[7,8]

Systemic side effects are uncommon; the most common being mild hypotension when using higher doses

Contraindications are few but include a history of hypersensitivity to alprostadil, a risk of priapism and bleeding disorders.

Summary of efficacy data in proposed use:

MHRA marketing authorisation was granted by Mutual Recognition on 17th July 2015.

Pivotal studies

Treating men with predominantly nonpsychogenic erectile dysfunction with intracavernosal vasoactive intestinal polypeptide and phentolaminemesylate in a novel auto-injector system: a multicentre, double blind, placebo controlled study. Dinsmore (1999)[9]

This study was conducted between March 1996 and December 1997 and was divided into a dose assessment phase (DAP) and a placebo controlled phase (PCP) of 6 months duration. During the DAP, 193 of the 236 men had a Grade III erection with either of the two doses 25micrograms VIP / 1mg phentolamine (VIP/P-1) (129 men) or 25micrograms VIP / 2mg phentolamine (VIP/P-2) (42 men) supplied in 0.35ml via auto-injector (the auto-injector is not currently licensed / available in the UK). The VIP/P-2 dose was only used in those men who did not achieve a satisfactory response to VIP/P-1. Before commencing the PCP, 22 of the 193 responders withdrew or were withdrawn, one for an adverse event and 21 for other reasons. 171 patients were therefore enrolled in the PCP, 30 never used a single

injector and were removed from the analysis.

Of 141 patients, 136 received at least one injection of active drug and placebo and were analysed by intention to treat; 105 met the full protocol completion criteria. 49 patients who initiated therapy in the PCP withdrew or were withdrawn (6 due to adverse events), an additional 17 did not meet the full protocol analysis criteria but were not withdrawals. Differential analysis of active drug vs placebo by underlying aetiology showed no statistical difference in efficacy of either VIP/P-1 or VIP/P-2.

In the per protocol analysis of active injections, VIP/P-1 and VIP/P-2 produced a Grade III erection in 75% and 66% of men respectively, with corresponding placebo responses of 12% and 18%.

In the intention to treat analysis of VIP/P-1 and VIP/P-2, active injections produced a Grade III erection in 73% and 69% of patients respectively with corresponding placebo responses of 12% and 15%.

A double blind, placebo controlled study of intracavernosal vasoactive intestinal polypeptide and phentolaminemesylate in a novel auto-injector for the treatment of non –psychogenic erectile dysfunction. Sandhu (1999)[10]

This study was conducted between January 1996 and December 1997 and was divided into a Dose Assessment Phase and two Placebo Controlled Phases, each of six months duration. In the Dose Assessment Phase, 304 men who met the entry criteria were administered VIP/P-1 (25 micrograms VIP and1.0mg phentolamine in 0.35 ml) in the clinic by the investigator utilizing the auto-injector.

A Grade 3 erection achieved in response to this test dose allowed the patient to be immediately admitted to the Placebo Controlled Phase. Patients who failed to respond adequately to in clinic VIP/P-1 were given two active auto-injectors for self-administration at home. The first contained VIP/P-1 and the second VIP/P-2 (25 micrograms VIP and2.0mg phentolamine in 0.35 ml). Patients were instructed to keep a diary and report any response to the injection and any adverse events. Patients who achieved a grade three erection to in home VIP/P-1 were allowed to enter the Placebo Controlled Phase, and the unused VIP/P-2 auto injector was returned. Patients who did not achieve a satisfactory response to VIP/P-1 were told to administer the VIP/P-2 dose after a minimum 36h waiting period. Patients who achieved a grade three erection with VIP/P-2 were allowed to enter the Placebo Controlled Phase; any other response was considered a treatment failure, entered into the study data and analysed, the patient being withdrawn from the study. During the dose assessment phase 255 out of 304 men had a grade three erection for an overall response rate of 83.9% with either of the two doses. Prior to commencing the Placebo Controlled Phase, 15 responders withdrew, so two hundred and forty patients were enrolled into Placebo Controlled 1. Forty-five of these patients never used a single injector and were withdrawn as non-protocol compliant. 172 out of 195 (88.2%) patients received at least one injection of active and placebo and could be analysed under intention to treat, 133 (68.2%) met full Placebo Controlled 1 protocol completion criteria. Of the 133 patients completing Placebo controlled 1, 126(94.7%) participated in Placebo controlled 2 sufficiently for intention to treat analysis, 105 (79.3%) completing the full Placebo controlled 2 protocol. The total drop out rate 199 / 304 (65.5%) was considerably higher than in other alprostadil trials, there are no explanatory comments giving reasons for this high drop out rate.[11]

Differential analysis of active vs placebo by underlying aetiology demonstrated no statistical difference in efficacy of either VIP/P-1 or VIP/P-2.

Within this trial was a subset of patients (183) who had previously withdrawn from one or more previous ED therapies. Of these 106 had previously been treated with alprostadil and a cumulative response rate of 59.4% and 81.1% was found when treating these patients with VIP/P-1 and VIP/P-2 respectively.

Whether analysed per protocol or intention to treat, there was significant difference ($P<0.001$) between active and placebo when examining separately both VIP/P-1 and VIP/P-2. In the per protocol analysis of VIP/P-1 and VIP/P-2, active injections produced an

erection suitable for intercourse in 75.1% and 66.5% respectively, with corresponding placebo responses of 12.2% and10.3%. In the intention to treat analysis of VIP/P-1and VIP/P-2, active injections produced an erection suitable for intercourse in 73.7% and 69.1% respectively, with corresponding placebo responses of 12.9% and 13.7%.

Injection therapy for the treatment of erectile dysfunction: a comparison between alprostadil and a combination of vasoactive intestinal polypeptide and phentolamine mesylate. Shah (2007)[12]

This was an open label, multicentre randomised crossover study designed to compare efficacy and tolerability of aviptidil / phentolamine and alprostadil, and to evaluate patient preference for these treatments. Patients received aviptidil in combination with phentolamine; each at a range of doses (12.5 or 25 micrograms of aviptadil and 0.5, 1.0 or 2.0 mg of phentolamine, respectively). Patients received alprostadil at doses of 5–20 micrograms. All treatments were self-administered.

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 in each patient. Patients who did not achieve an adequate response to either treatment were not eligible for phase 2 of the study. 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 autoinjector, 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.

In phase 1, 187 patients received treatment. Significantly fewer patients achieved a grade 3 erection after treatment with aviptadil/phentolamine than after treatment with alprostadil (137 [73%] and 155 [83%] respectively).

In phase 2, results were reported for the total number of injections. The percentages 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 51 patients in phase 1 and 67 patients in phase 2. In both phases, significantly more patients preferred one of the aviptadil/phentolamine preparations over alprostadil. In phase 2 of the study, 73% of patients preferred the aviptadil/phentolamine auto-injector preparation (not currently licensed in the UK), whilst 19% preferred the licensed aviptadil/phentolamine preparation and 8% preferred alprostadil.

The conclusion was that both VIP/ phentolamine and alprostadil were effective treatments for ED. This conclusion is based on results from the comparative section of the study (phase 2). However, the comparative phase excluded patients who did not respond to treatment with either aviptadil/phentolamine or alprostadil. Results of the earlier dose-finding phase of the study, which included all patients recruited into the study, show that significantly fewer patients achieved a grade 3 erection with aviptadil/phentolamine than with alprostadil. The first phase of the study was primarily a dose-response phase and would therefore not necessarily have been optimally conducive to a natural sexual response. However, phase 2 of the trial also reported some differences in the adverse event profiles of the two treatments. It is therefore unclear whether the clinical effectiveness of aviptadil/phentolamine is equivalent to alprostadil.

Vasoactive intestinal polypeptide and phentolamine mesylate administered by autoinjector in the treatment of patients with erectile dysfunction resistant to other intracavernosal agents.Dinsmore (1998)[13]

A small study conducted in 70 consecutive patients, in whom previous therapy with intracavernosal prostaglandin E1 (alprostadil) 20 micrograms and papaverine (30mg) combined with 1mg Phentolamine mesylate had failed, were given intracavernosal

injections initially with VIP/P-1 and if unsuccessful VIP/P-2, via an auto-injector device. Forty seven (67%) of patients achieved erections sufficient for sexual intercourse, 33 on VIP/P-1 and 14 (of the 37 patients who failed on VIP/P-1) on VIP/P-2.

Overall Conclusions on the clinical efficacy

In the Dinsmore trial (1999)[9] differential analysis of active drug vs placebo by underlying aetiology showed no statistical difference in efficacy of either VIP/P-1 or VIP/P-2.

In the Sandhu trial (1999)[10] differential analysis of active drug vs placebo by underlying aetiology showed no statistical difference in efficacy of either VIP/P-1 or VIP/P-2. Whether analysed per protocol or intention to treat, there was significant difference (P<0.001) between active and placebo when examining separately both VIP/P-1 and VIP/P-2. In the per protocol analysis of VIP/P-1 and VIP/P-2, active injections produced an erection suitable for intercourse in 75.1% and 66.5% respectively, with corresponding placebo responses of 12.2% and 10.3%. In the intention to treat analysis of VIP/P-1 and VIP/P-2, active injections produced an erection suitable for intercourse in 73.7% and 69.1% respectively, with corresponding placebo responses of 12.9% and 13.7%. Within this trial were a subset of patients (183) who had previously withdrawn from one or more previous ED therapies. Of these 106 had previously been treated with alprostadil and a cumulative response rate of 59.4% and 81.1% was found when treating these patients with VIP/P-1 and VIP/P-2 respectively.

In the Shah trial, VP007, (2007)[12] in phase 1, 187 patients received treatment. Significantly fewer patients achieved a grade 3 erection after treatment with aviptadil/phentolamine than after treatment with alprostadil (137 [73%] and 155 [83%] respectively).

Following phase 2, the paper concludes that the efficacy of aviptadil/phentolamine is similar to alprostadil. However, patients received a range of doses of aviptadil and phentolamine (12.5 or 25 micrograms and 0.5, 1.0 or 2.0 mg, respectively), either prepared from ampoules or administered in an auto-injector. Therefore not all patients received aviptadil/phentolamine as the licensed (25 micrograms/2 mg) dose and formulation. Similarly, patients received alprostadil at doses of 5–20 micrograms, and although the SPC states that the majority of patients achieve a satisfactory response within this dose range, doses of up to 60 micrograms can be used[14]. Therefore, it is unclear whether the doses used in VP 007 are fully representative of clinical practice for either medicine.

The study used two aviptadil/phentolamine preparations, only one of which (ampoules) is licensed in the UK. The results of this study indicate a significant patient preference for aviptadil/phentolamine over alprostadil. However, in phase 2 of the study the majority of patients preferred the unlicensed aviptadil/phentolamine auto-injector preparation.

The study is described as a randomised crossover study, but no detail is reported of how patients crossed over from one treatment to another. Patients were only eligible for the comparative phase of the study if they achieved a grade 3 erection with both study treatments, meaning that this phase of the study is likely to overestimate the effectiveness of both treatments. Furthermore, 130 patients completed phase 1, but only 107 patients started phase 2. Reasons for patients dropping out of the study are not explained. Grade 3 erections are reported per patient in phase 1 but per injection in phase 2; the reason for this discrepancy is also not explained, and the total number of patients for whom results were available in phase 2 is not clear.

In the small study conducted by Dinsmore (1998)[13] it was demonstrated that the combination of VIP and phentolamine mesylate is an effective therapeutic option in patients unresponsive to conventional intracavernosal therapy.

Summary of safety data:

In the Dinsmore trial (1999),[9] during the DAP, 98 of the 236 patients (42%) reported a total of 191 adverse events most of which were categorised as mild to moderate. Related events included flushing (40%), bruising (8%), tachycardia / palpitations (8%), headache (4%), bleeding at the injection site (3%), pain on injection (2%) and dizziness (2%).

During the PCP, a total of 1473 injection for which diary entries were completed in 141 patients were analysed for adverse events, the major adverse event was facial flushing (47% of VIP/P-1 and 50% of VIP/P-2 injections), bruising (5.5% and 7.2% respectively), bleeding at injection site (4.6% and 4% respectively), urethral bleeding (2.5% and 2.2% respectively), palpitations (2% and 0.7% respectively) and tachycardia (2.1% and 3.2% respectively). There was a single episode of priapism. No patient on active therapy complained of pain after injection.

In the Sandhu trial (1999),[10] the majority of patients (74.4%) in the Placebo Controlled Phase noted mild transient flushing, the incidence per injection decreased to 33.8% and this resulted in no patients withdrawing from this part of the study. In 3 out of 304 patients (1.0%) in the Dose Assessment Phase facial flushing contributed to withdrawal, whereas the overall incidence of flushing was 7.9%. Minor urethral bleeding was noted following 1.4% of active injections and 1.0% of placebos and is possibly related to injection technique. There were two episodes of priapism in 304 patients, the incidence per injection in the Placebo Controlled Phase being 0.05%. There were no reports of pain on injection, however, in this trial the injection was delivered via the auto-injector which is not currently licensed in the UK.

16.1% of patients withdrew because of treatment failure and 2.9% patients due to adverse events.

In the Shah trial VP007 (2007),[12] significantly fewer patients in the comparative phase reported pain with aviptadil/phentolamine ampoules than with alprostadil (3 vs 28 reports of pain per 100 injections/patient, respectively). In the comparative phase, 49 (46%) and 32 (30%) patients reported an adverse event with alprostadil and aviptadil/phentolamine ampoules, respectively; 15 (14%) and 6 (6%) patients respectively reported a moderate or severe adverse event. In the earlier dose-finding phase, 86 (46%) and 57 (30%) of patients reported an adverse event with alprostadil and aviptadil/phentolamine ampoules, respectively; 23 (12%) and 8 (4%) of patients respectively reported a moderate or severe adverse event.

Compared with alprostadil, aviptadil/phentolamine injection was associated with significantly fewer incidences of pain (28 versus 3 cases per 100 injections, respectively, $p<0.001$), but significantly more incidences of facial flushing (3 versus 17 cases per 100 injections, respectively, $p < 0.001$). No cases of priapism were reported with either treatment.

In the Dinsmore study (1998),[13] the most commonly experienced adverse events were facial flushing (37% of patients), bruising (14%), injection pain (8%) and truncal flushing (6%)

The Summary of Product Characteristics states that approximately 10% of patients experienced adverse reactions to aviptadil/phentolamine.[1]

Undesirable Effects listed as below:[1]

Nervous System disorders Uncommon (≥ 1/1000 to <1/100)	 Headache, dizziness
Cardiac disorders Uncommon (≥ 1/1000 to <1/100) Very Rare (<1/10,000)	 Tachycardia, palpitations Myocardial Infarction, angina pectoris
Vascular disorders Common (≥ 1/100 to < 1/10)	 Flushing

Reproductive system and breast disorders Rare (≥1/10,000 to < 1/1000)	Priapism, prolonged erection, penile nodules / fibrosis following multiple injections
General disorders and administration site conditions Common (≥ 1/100 to < 1/10) Uncommon (≥ 1/1000 to <1/100) Rare (≥1/10,000 to < 1/1000)	 Bruising Haematoma Pain post injection

Strengths and limitations of the evidence:

Strengths:

- Active comparator arm as well as placebo

Limitations:

- SPC not available on eMC
- 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.

Prescribing and risk management issues:

HSC/148 advises doctors that one erectile dysfunction treatment per week will be appropriate for most patients. If the GP, in exercising their clinical judgement, considers more than one treatment a week is appropriate, they should prescribe that amount on the NHS.[6]

Correct injection technique is important and Invicorp should **not** be prescribed without adequate instruction and training in its use.

The Summary of Product Characteristics states:

Prolonged erection and/or priapism may occur following intracavernosal administration of Invicorp. Patients should be instructed to immediately report to a physician any erection lasting for a prolonged period, such as 4 hours or longer.

Treatment of priapism should not be delayed more than 6 hours. Treatment of priapism should be according to established medical practice

Penile fibrosis, including angulation, cavernosal fibrosis, fibrotic nodules and Peyronie's disease may occur following the intracavernosal administration of Invicorp. The occurrence of fibrosis may increase with increased duration of use.

Regular follow-up of patients, with careful examination of the penis, is strongly recommended to detect signs of penile fibrosis or Peyronie's disease. Fibrosis has been rarely reported with the prolonged use of other intracavernosal pharmacotherapies. Whilst not so far observed on Invicorp, the possibility of an association must be considered. Treatment with Invicorp should be discontinued in patients who develop penile angulation, cavernosal fibrosis, or Peyronie's disease.

Mild transient flushing of the face or trunk occurs commonly. This is rarely associated with discomfort and palpitations or tachycardia in which cases patients may be withdrawn from treatment.

Commissioning considerations:

Alprostadil is currently the main drug available in the UK for intracavernosal injection.

Prescribing of Alprostadil across Lancashire March 2016 to February 2017

BNF Name	BLACKBURN WITH DARWEN CCG	BLACKPOOL CCG	CHORLEY AND SOUTH RIBBLE CCG	EAST LANCASHIRE CCG	FYLDE & WYRE CCG	GREATER PRESTON CCG	MORECAMBE BAY CCG	WEST LANCASHIRE CCG	Total Items
Alprostadil	262	386	294	720	383	312	435	218	3010
Phentolamine/Aviptadil	0	0	0	0	0	0	0	0	0
Total Items	**262**	**386**	**294**	**720**	**383**	**312**	**435**	**218**	**3010**
Alprostadil	£11,915.58	£20,408.60	£11,673.12	£35,850.76	£18,839.77	£15,562.46	£21,048.95	£9,081.25	£144,380.49
Phentolamine/Aviptadil	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
Total Act Cost	**£11,915.58**	**£20,408.60**	**£11,673.12**	**£35,850.76**	**£18,839.77**	**£15,562.46**	**£21,048.95**	**£9,081.25**	**£144,380.49**

The cost per injection of Invicorp is the same as the cost per injection of Caverject 20micrograms Dual Chamber (£9.50). However, none of the trials demonstrated the therapeutic equivalence of these two drugs at these doses. In the pivotal trial (2007) despite an overall dose response trend, some patients who responded to the higher dose of aviptadil / phentolamine (25micrograms / 2mg) also responded to lower doses of alprostadil.

It is therefore difficult to determine whether the prescribing of Invicorp for those patients not responding or intolerant to Alprostadil (Caverject), as an option before referral for surgical procedure will be cost neutral.

Anticipated patient numbers and net budget impact

Due to the nature of ED and its change in prevalence with increasing age and presence of co-morbidities it is very difficult to estimate anticipated patient numbers across Lancashire.

The applicant has suggested that there would be approximately 20 patients per year eligible for Invicorp treatment (patients not responding or intolerant to Alprostadil (Caverject), as an option before referral for surgical procedure) within the catchment area of Blackpool Teaching Hospitals NHS Foundation Trust. According to the NICE resource impact template the population of Blackpool CCG is 140,501.

20 patients therefore represent 0.014% of the total population.

For the initial AWMSG appraisal recommendation (3216)[15], the manufacturer suggested that approximately 530 men in Wales are likely to be suitable to receive treatment with Invicorp annually with an uptake within the eligible population of initially 10% i.e. 53 patients, increasing to 30% by year 5 – they assumed the population of Wales to be 3.4 million. 530 men represent 0.0156% of the total population.

The slight discrepancy might be due to the fact that the applicant is looking to reserve use to those patients not responding or intolerant to Alprostadil (Caverject), as an option before referral for surgical procedure, whilst the AWMSG submission considered Invicorp as second line therapy in patients with ED who do not respond to oral treatment with PDE5 inhibitors.

Associated additional costs or available discounts:

None identified

Productivity, service delivery, implementation:

Correct injection technique is important and Invicorp should not be prescribed without adequate instruction and training in its use. Initial injections must be administered by medically trained personnel.[1,16]

The manufacturer advises regular monitoring (e.g. every 3 months) particularly in the initial stages of self-injection therapy. [1]

Invicorp needs to be stored in a refrigerator (2-8^{o}C)[1]

Innovation, need, equity:

As per application, Aviptadil / Phentolamine (Invicorp) is an alternative therapy for those patients not responding or intolerant to Alprostadil (Caverject), as an option before referral for surgical procedure

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: high quality randomised controlled trials (RCTs) with low risk of bias systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: clinical trials at moderate or high risk of bias systematic reviews or meta-analyses of such clinical trials or with inconsistent findings cohort studies case-control studies	
Level 3	Disease-oriented evidence, or evidence from: consensus guidelines expert opinion case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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[16] British National Formulary https://www.medicinescomplete.com/mc/bnf/current/DMD30737111000001103.htm?q=invicorp&t=search&ss=text&tot=3&p=1#DMD30737111000001103 (accessed online 17th May 2017)