I. Appendix 9: Intracavernous Injections for Erectile Dysfunction (ED)

A. RCTs only, single-dose studies

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Drugs and Doses</th>
<th>Study Design, Duration and Size</th>
<th>Participants and Etiology of Impotence</th>
<th>Outcomes</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linet (1996)</td>
<td>Alprostadil (PGE1) 2.5 µg, 5 µg, 10 µg, 20 µg or placebo.</td>
<td>Multi-center, randomized, double blind, placebo-controlled, single fixed dose, parallel group. Dose administered in clinic by researcher.</td>
<td>Inclusions: ED of vasculogenic, neurogenic, psychogenic or mixed origin; duration of ED &gt; 4 months. Exclusions: penile deformity; history of priapism; sickle-cell trait; recent major illness; uncontrolled diabetes or hypertension; major psychiatric disorder; infection with HIV or &quot;other transmittable disease&quot;; smoking &gt; 40 cigs/day; endocrine etiology of ED.</td>
<td>RigiScan response defined as &gt; 70% rigidity at tip or base of penis lasting &gt; 10 consecutive minutes. Clinical response defined as penile rigidity sufficient for intercourse as assessed by researcher palpation. No response to placebo. For both outcomes the differences between each dose of PGE1 and placebo were statistically significant (p &lt; 0.01). There was a statistically significant dose-response relationship for clinical response (p &lt; 0.001) but not RigiScan response.</td>
<td>DOSE-RESPONSE PGE1 (all doses): Penile pain 23%, Priapism 1%, Prolonged erection 3%, Placebo: No data given.</td>
</tr>
</tbody>
</table>

| Colli (1996) | PGE1 5 µg, 10 µg or placebo. | Single center, randomized, double blind, placebo-controlled, fixed single dose administered by researcher, cross-over study (1 week washout). | Inclusions: ED > 6 months Exclusions: Penile deformity; history of priapism; low free testosterone; elevated prolactin; BP > 150/100 or hypotension; smoking > 40 cigs/day; uncontrolled diabetes; sickle cell disease; coagulopathy; systemic or psychiatric disease of recent onset; hemoglobin disease; current use of intracavernous PGE1. | Erectile response outcomes included: (1) reaching and maintaining 70% rigidity per RigiScan for > 10 minutes at tip or base of penis; (2) researcher palpation and rating of erection as “full”; and (3) subject rating of erection as “good” or “excellent”. | Penile pain: Placebo 0%, PGE1 5 µg 39%, PGE1 10 µg 56%. Hematoma: Placebo 0%, PGE1 5 µg 2%, PGE1 10 µg 0%. |
### Adverse Events
- **Prolonged erections:**
  - Placebo: 0%
  - PGE1: 15%
  - PP: 18%

- **Pain:**
  - Placebo: 0%
  - PGE1: 35% *
  - PP: 15% *
  * (p < 0.05 vs placebo)

- **Penile pain:**
  - PPP: 15%
  - PP: 0%

- **Erection > 60 mins:**
  - PPP: 10%
  - PP: 5% (p < 0.05)

---

### Study Design, Duration and Size
- **Single center, randomized, double blind, placebo-controlled, fixed single dose self-injected, cross-over study** (subjects received one dose of each treatment; 1 week washout).
  - Overall N=60 (100% completed)

- **Single center, randomized, patient-blind, active-controlled, fixed single dose, researcher injected, cross-over study** (≥1 week washout).
  - Overall N=32 (19 completed)

- **Single center, randomized, double blind, fixed single dose, administered by researcher, cross-over study** (washout 2 wks).
  - Overall N=20

---

### Drugs and Doses
- **PGE1 30 µg**
- **Papaverine 30 mg + Phentolamine 0.5 mg (PP)**
- **Placebo**

- **PGE1 40 µg**
- **PGE1 5.8 µg + Papaverine 17.6 mg + Phentolamine 0.6 mg (PPP)**

- **Papaverine 4.5 mg + Phentolamine 0.25 mg + PGE1 5 µg (PPP)**
- **Papaverine 9 mg + Phentolamine 0.5 mg (PP)**

---

### Participants and Etiology of Impotence
- **Inclusions:**
  - ED > 6 months

- **Exclusions:**
  - ED from spinal cord injury or radical pelvic surgery; treatment with vasoactive injections
  - Demographics:
    - Ages 22-78 (mean 58)

- **Inclusions:**
  - ED > 6 months; nonresponse to high doses of papaverine + phentolamine combo.
  - Demographics:
    - Ages 26 - 71 (mean 61.3)
    - ED duration (months):
      - Mean 30.8 (range 6-51)

- **Inclusions:**
  - Patients "newly entering our intracorporeal injection program"

- **Exclusions:**
  - None given
  - Demographics:
    - Ages 44 - 71 (mean 57.5)
    - Etiology of ED:
      - Arteriogenic: 60%
      - Neurogenic: 15%
      - Other: 25%

---

### Outcomes
- **Responses evaluated to manual and visual stimulation. Erections "allowing penetration" considered positive.**
  - Response rates:
    - Placebo: 0%
    - PGE1: 50%
    - PP: 56% (p > 0.05)

- **Erections defined as response at 15 minutes after dose adequate to "allow penetration" (rating categories stated but manner in which erections placed into categories not given)**
  - Erections:
    - PGE1: 22%
    - PPP: 50% (p < 0.05)

- **Erections rated by physician palpation 15 minutes after injection as either 'full', 'suboptimal... but sufficient for penetration' or 'not sufficient'**
  - Full erections:
    - PPP: 73%
    - PP: 28% (p < 0.05)

---

### Adverse Events
- **Prolonged erections:**
  - Placebo: 0%
  - PGE1: 15%
  - PP: 18%

- **Pain:**
  - Placebo: 0%
  - PGE1: 35% *
  - PP: 15% *
  * (p < 0.05 vs placebo)

- **Penile pain:**
  - PPP: 15%
  - PP: 0%

- **Erection > 60 mins:**
  - PPP: 10%
  - PP: 5% (p < 0.05)
### Study Name

**Vanderschuren (1995)**

- **Drugs and Doses:** 3 unique formulations of PGE1:
  1. Pediatric sterile solution
  2. Sterile powder
  3. Nonalcohol sterile solution

- **Study Design, Duration and Size:** Multi-centered, stratified [subjects using low doses of PGE1 at home prior to study (<10 µg) received one of 3 possible doses within the study: placebo, 2.5 µg PGE1 or 5 µg PGE1; subjects using high doses of PGE1 at home prior to study (>10 µg) were eligible to receive placebo, 10 µg PGE1 or 20 µg PGE1]. Randomized double blind, placebo-controlled, fixed single dose, cross-over (washout ≥ 3 days);

- **Participants and Etiology of Impotence:** Inclusions:
  - ED > 4 months; known stable responders to intracavernosal PGE1
  - Exclusions:
  - Penile deformity; Peyronie’s disease; history of priapism; “suffering from major diseases or took drugs that could substantially affect the evaluation of the ED.

- **Outcomes:**
  - Erectile response outcomes included:
    - (1) penile radial rigidity ≥ 70% for ≥10 minutes; (2) patient assessment, 0 = not effective to 3 = very effective; (3) investigator evaluation that erection is sufficient for vaginal penetration. For all these measures, there were no significant differences between the 3 formulations at any dose. (p > 0.1)

- **Adverse Events:**
  - Penile pain:
    - Placebo 11%
    - Pediatric solution 9%
    - Sterile powder 14%
    - Nonalcohol 17%

**Sogari (1997)**

- **Drugs and Doses:**
  - (1 = PPPA) PGE1 10 µg + papaverine 50 mg + Atropine 0.075 mg
  - (2 = PPP) PGE1 10 µg + papaverine 50 mg + Phentolamine 0.2 mg

- **Study Design, Duration and Size:** Single center, randomized, non-blinded, active-controlled, fixed single dose, parallel group study. Dose administered by researcher.

- **Participants and Etiology of Impotence:** Inclusions:
  - Consecutive ED patients seen in a Urology clinic
  - Exclusions:
  - Partial penile amputation

- **Outcomes:**
  - Erectile response assessed 15 minutes after injection by examiner palpation as "full erection", "poor erection", or "tumescence".
  - % with full erection:
    - PPPA 45.6%
    - PPP 45.6% (p = 1.0)

- **Adverse Events:**
  - Penile pain:
    - Placebo 11%
    - Pediatric solution 9%
    - Sterile powder 14%
    - Nonalcohol 17%

**Kattan (1995)**

- **Drugs and Doses:**
  - (1) PGE1 20 µg
  - (2) PGE1 20 µg + Lidocaine 1% (P + L)

- **Study Design, Duration and Size:** Single center, randomized, double blind, active-controlled, fixed single dose, administered by researcher, cross-over study (washout 1 week); Analysis not intention to treat.

- **Participants and Etiology of Impotence:** Inclusions:
  - Previously experienced pain with intracavernosal injections of PGE1
  - Exclusions:
    - MI; uncontrolled hypertension

- **Outcomes:**
  - Investigator rated erection as "normal", "adequate", "inadequate" or "none".
  - % adequate or normal erections:
    - PGE1 27.2%
    - P + L 63.6% (p < 0.01)

- **Adverse Events:**
  - Penile pain:
    - Placebo 11%
    - Pediatric solution 9%
    - Sterile powder 14%
    - Nonalcohol 17%
### B. Long-term RCTs only

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Drugs and Doses</th>
<th>Study Design, Duration and Size</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buvat (1998)</td>
<td>Alprostadil alpha-cyclodextrin 5-20 µg or Moxisy late chlorhydrate 5-20 mg.</td>
<td>Multi-centered, active-control, parallel-group study of self-injections</td>
<td>Inclusions:</td>
<td>Erectile response outcomes in clinic were: (1) “buckling test,” and (2) physician evaluation of adequacy of erection for intercourse. Only outcomes from the at-home phase are detailed here:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DOSING PHASE</td>
<td></td>
<td>% of subjects with at least 1 rigid erection after self-injection:</td>
<td>Penile pain during injection(%): CL AH: Alprostadil 13 25 Moxisy late 15 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subjects were randomized to either Alprostadil or Moxisy late. Optimal treatment dose was</td>
<td></td>
<td>Alprostadil* 85</td>
<td>Penile pain during erection(%): CL AH: Alprostadil* 17 24 Moxisy late 3 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>determined via double blinded in-clinic titration. OPEN-LABEL PHASE</td>
<td></td>
<td>Moxisy late 61</td>
<td>Penile pain after erection(%): CL AH: Alprostadil* 7 19 Moxisy late 0 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Responders from dosing phase performed up to 6 at-home self-injections of the treatment to</td>
<td></td>
<td>Mean % successful self-injections:</td>
<td>Bleeding(%): CL AH: Alprostadil 3 15 Moxisy late 3 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>which they had been randomized in the dosing phase. Dose was that determined in the dosing</td>
<td></td>
<td>Alprostadil* 61</td>
<td>Erection &gt; 2 hours: CL AH: Alprostadil 5 4 Moxisy late 0 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phase as their optimum dose.</td>
<td></td>
<td>Moxisy late 44</td>
<td><em>(p&lt;0.05)</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>186 subjects screened; 156 randomized in dosing phase:</td>
<td></td>
<td>Mean score subject’s opinion of treatment on visual analog scale (scale is 0-100; 0=treatment does not suit me at all to 100=treatment suits me perfectly): Alprostadil* 52.8 Moxisy late 36.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alprostadil=75; Moxisy late=81;</td>
<td></td>
<td>* (p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>129 achieved adequate response in dosing phase by at least one measure: Alprostadil=68/75;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moxisy late=61/81; The 129 responders were enrolled in open-label at-home phase. Follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>in open-label phase was complete.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration of ED, mean years:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alprostadil 4.6; Moxisy late 4.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Etiology of ED (%):ʻ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psycho-genic Alprostadil 51 27 23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Organic Mixed Moxisy late 43 26 32</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ED = erectile Dysfunction  CL = in-clinic  AH = at-home
### Adverse Events
- **Bruising, injury or skin changes sufficient to stop or decrease treatment (%):**
  - Injection: 9
  - Vacuum: 16

- **Penile pain:** “experienced rarely”

- **Priapism:** 1 patient had priapism after first injection (treatment arm not specified) and withdrew.

### Outcomes
- **Erectile response outcomes included:**
  1. Patient satisfaction “with the sexual experience” on a scale of 0-10
  2. Partner satisfaction “with the sexual experience”
  3. Patient preference for one method over the other

#### Patient satisfaction:
- Injection: 6.5
- Vacuum: 5.4 (p<0.05)

#### Partner satisfaction:
- Injection: 6.5
- Vacuum: 5.1 (p<0.05)

#### Patient preference (%):
- Injection: 57
- Vacuum: 27
- Both: 14
- None: 2

#### Partner preference (%):
- Injection: 50
- Vacuum: 27
- Both: 14
- Neither: 9

Subgroup analysis suggests injection superior to vacuum in subjects with ED of shorter duration or secondary to radical prostatectomy (p<0.05).

### Study Design, Duration and Size
- Single center, quasi-randomized (by social security number), nonblinded, active-controlled, crossover study (no washout described)
- Each treatment used at least 15 times
- N=50 (44 completed study)

### Participants
- **Inclusions:**
  - Previously untreated organic impotence
  - Stable sexual partnership
  - Using testosterone replacement
  - Psychogenic etiology
  - Failure to respond with erection “satisfactory for penetration” to either injection or vacuum while in office
  - Stated preference for 1 of the treatments
- **Exclusions:**
  - Age, mean yrs (range): Overall 62.3 (38-84)
  - Duration of ED, mean mos. (range): Overall 40 (6-120)
- **Etiology of ED (%):**
  - Vascular: 30
  - Surgical: 26
  - Diabetes: 18
  - Unknown: 14

### Drugs and Doses
- **(1) Alprostadil** 1.5µg + Papaverine 4.4mg + Phentolamine 0.15mg (Trimex)
- **(2) External vacuum device (Osbon ErecAid)**
### C. Abstracts

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Drugs and Doses</th>
<th>Study Design, Duration and Size</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Su (1998)</td>
<td>Intracavernous injection of Alprostadil 5µg or 10µg; or Transurethral Alprostadil 500µg or 1000µg.</td>
<td>Randomized, active controlled, crossover study (washout not specified)</td>
<td>Inclusions: Men with organic erectile dysfunction. Exclusions: Not given</td>
<td>Overall treatment preference (%): Injection 64 Transurethral 36 Quality of erection as assessed by subject, scale from 0=(no erection) to 5=(rigid, adequate for penetration): Comparison 1: Injection 5µg vs. Transurethral 500µg</td>
<td>No information given.</td>
</tr>
</tbody>
</table>

```
Comparison 1: Injection 5µg vs. Transurethral 500µg
Injection * 2.8
Transurethral 1.5
```

```
Comparison 2: Injection 10µg vs. Transurethral 1000µg
“no statistical difference”
```

```
Subject satisfaction, scale from 0-5:
Injection 5µg * 3.2
Transurethral 500µg 1.5
```

* (p<0.01)
II. Appendix 10: Impotence Treatments [RCTs (33 articles, 18 abstracts)]

Oral (16 articles, 13 abstracts)

Apomorphine


Phentolamine [Vasomax] vs. placebo (1 article, 2 abstracts)


Goldstein, I. Efficacy and safety of oral phentolamine (Vasomax) for the treatment of minimal erectile dysfunction. Journal of Urology. 1998; 159(suppl):240 [meeting abstract #919].

Sildenafil vs. placebo (3 articles, 8 abstracts)


**Trazodone** vs. placebo (2 articles, 2 abstracts)


vs. testosterone vs. hypnosis vs. placebo (1 article)


**Trazodone + yohimbine** vs. placebo (1 article)


**Yohimbine** (1 systematic review / meta-analysis)


vs. placebo (8 articles)


Yohimbine / Isoxsuprine vs. pentoxifylline (1 article)


Transdermal (1 article, 1 abstract)

Aminophylline / Isosorbide dinitrate / Co-dergocrine mesylate


Injection (9 articles)

Alprostadil [PGE1] vs. placebo (3 articles)


vs. moxisylyte chlorhydrate (1 article)


vs. papaverine/phenolamine (1 article)


vs. PGE1/Lidocaine (1 article)


vs. PGE1/papaverine/phenolamine (1 article)


Prostaglandin E1/Papaverine/Phentolamine vs. Papaverine/Phentolamine (1 article)


Prostaglandin E1/Papaverine/Phentolamine/Atropine vs. PPP (1 article)


Intraurethral (5 articles, 4 abstracts)

Alprostadil vs. placebo (4 articles, 2 abstracts)


vs. prazosin vs. alprostadil/prazosin (1 abstract)


vs. prazosin vs. alprostadil/prazosin vs. placebo (1 article, 1 abstract)
