### 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>
</table>
| Linet (1996)  | Alprostadil (PGE1) 2.5 µg, 5 µg, 10 µg, 20 µg or placebo. | Multi-center, randomized, double blind, placebo-controlled, single fixed dose, parallel group. Dose administered in clinic by researcher.  
Overall N=296 (100% follow-up)  
Placebo n=59  
PGE1 2.5 µg n=57  
PGE1 5 µg n=60  
PGE1 10 µg n=62  
PGE1 20 µg n=68 | Inclusions:  
ED of vascular origin, neurogenic, psychogenic or mixed origin; duration of ED ≥ 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 “other transmissible disease”; smoking > 40 cigs/day; endocrine etiology of ED.  
Demographics:  
Ages 21 - 74 (mean 54)  
Etiology of ED:  
Vascular 44%  
Psychogenic 14%  
Neurogenic 13%  
Mixed 29%  
Previous therapy for ED:  
2% had prior injection treatment | RigiScan response defined as >70% rigidity at tip or base of penis lasting > 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<0.01). There was a statistically significant dose-response relationship for clinical response (p<0.001) but not RigiScan response. | DOSE-RESPONSE  
PGE1 (all doses):  
Penile pain 23%  
Priapism 1%  
Prolonged erection 3%  
Placebo:  
No data given |
| 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).  
Overall N=296 (100% follow-up)  
Placebo n=59  
PGE1 2.5 µg n=57  
PGE1 5 µg n=60  
PGE1 10 µg n=62  
PGE1 20 µg n=58 | 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.  
Demographics:  
Ages 18 - 65 (mean 54)  
Etiology of ED:  
Vascular 27%  
Psychogenic 53%  
Mixed 11%  
Neurogenic 4%  
Diabetes 4% | 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’.  
RigiScan:  
Placebo 0%  
PGE1 5 µg 39%  
PGE1 10 µg 56%  
Researcher palpation:  
Placebo 0%  
PGE1 5 µg 27%  
PGE1 10 µg 51%  
Subject rating:  
Placebo 0%  
PGE1 5 µg 41%  
PGE1 10 µg 56% | Penile pain 0%  
PGE1 5 µg 0%  
PGE1 10 µg 7%  
Hematoma:  
Placebo 0%  
PGE1 5 µg 2%  
PGE1 10 µg 0% |
### Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>PGE1</th>
<th>PP</th>
<th>PGE1</th>
<th>PPP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prolonged erections:</strong></td>
<td>0%</td>
<td>18%</td>
<td>12%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Pain:</strong></td>
<td>0%</td>
<td>35%</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td><em>p &lt; 0.05 vs placebo</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Outcomes

**Responses evaluated to manual and visual stimulation. Erections "allowing penetration" considered positive.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>PGE1</th>
<th>PP</th>
<th>PGE1</th>
<th>PPP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rates:</strong></td>
<td>0%</td>
<td>50%</td>
<td>56%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td><em>p &lt; 0.05</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PGE1</th>
<th>PPP</th>
<th>PGE1</th>
<th>PPP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erections:</strong></td>
<td>22%</td>
<td>50%</td>
<td>28%</td>
<td>50%</td>
</tr>
<tr>
<td><em>p &lt; 0.05</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Erections rated by physician palpation 15 minutes after injection as either ‘full’, ‘suboptimal’, ‘but sufficient for penetration’ or ‘not sufficient’.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PPP</th>
<th>PP</th>
<th>PPP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penile pain:</strong></td>
<td>15%</td>
<td>28%</td>
<td>15%</td>
</tr>
<tr>
<td><em>p &gt; 0.05</em></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Erections > 60 mins:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PPP</th>
<th>PP</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Penile pain:</strong></td>
<td>10%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td><em>p &gt; 0.05</em></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Study Name

**Vanderschuren (1995)**

- **Drugs and Doses**: 3 unique formulations of PGE1:
  - (1) pediatric sterile solution, (2) sterile powder, (3) nonalcohol sterile solution. For each formulation the following doses were available: PGE1 2.5 µg, 5 µg, 10 µg, 20 µg and placebo.
  - **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%

- **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)
  - N=210 (11 dropouts)

**Sogari (1997)**

- **Inclusions**: Consecutive ED patients seen in a Urology clinic
- **Exclusions**: Partial penile amputation
- **Demographics**:
  - Ages in years [mean (range)]:
    - PPA: 53.2 (24 - 75)
    - PPP: 52.7 (22 - 78)
  - Mean ED duration in months:
    - PPA: 32.2 (range 1 - 240)
    - PPP: 33.5 (range 2 - 360)
  - Comorbid conditions:
    - No difference between treatment groups in number of risk factors for ED, or in prevalence of any individual risk factors except stroke.

**Kattan (1995)**

- **Inclusions**: Previously experienced pain with intracavernosal injections of PGE1
- **Exclusions**: MI; uncontrolled hypertension
- **Demographics**:
  - Ages 40-60 (mean 53)

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### Study Name

**Vanderschuren (1995)**

- **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)

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<th>Outcomes</th>
<th>Adverse Events</th>
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| Vanderschuren (1995) | 3 unique formulations of PGE1:  (1) pediatric sterile solution, (2) sterile powder, (3) nonalcohol sterile solution. For each formulation the following doses were available: PGE1 2.5 µg, 5 µg, 10 µg, 20 µg and placebo. | 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) | Inclusions:
  - ED > 4 months; known stable responders to intracavernous 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.
  - **Demographics**:
    - Ages: 29 - 70 (mean 53.1)
    - ED duration (years):
      - Mean 4.8 (range 0.5-41)
    - Etiology of ED:
      - Vasculogenic: 21%
      - Psychogenic: 36%
      - Neurogenic: 7%
      - Diabetes: 7%
      - Other: 15% | 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) Penile pain:
  - Placebo: 11%
  - Pediatric solution: 9%
  - Sterile powder: 14%
  - Nonalcohol: 17% |

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**Sogari (1997)**

- **Inclusions**: Consecutive ED patients seen in a Urology clinic
- **Exclusions**: Partial penile amputation
- **Demographics**:
  - Ages: 40-60 (mean 53)

**Kattan (1995)**

- **Inclusions**: Previously experienced pain with intracavernosal injections of PGE1
- **Exclusions**: MI; uncontrolled hypertension
- **Demographics**:
  - Ages: 40-60 (mean 53)
B. Long-term RCTs only

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<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Buvat (1998)</strong></td>
<td>Alprostadil alpha-cyclodextrin 5-20 µg or Moxisylyte chlorhydrate 5-20 mg</td>
<td>Multi-centered, active-control, parallel-group study of self-injections</td>
<td></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>Penile pain during injection(%): CL AH Alprostadil* 13 24 Moxisylyte 15 15 Penile pain during erection(%): CL AH Alprostadil* 17 24 Moxisylyte 3 5 Penile pain after erection(%): CL AH Alprostadil* 7 19 Moxisylyte 0 5 Bleeding(%): CL AH Alprostadil 3 15 Moxisylyte 3 5 Erection &gt; 2 hours: CL AH Alprostadil 5 4 Moxisylyte 0 2 *(p&lt;0.05)</td>
</tr>
</tbody>
</table>

**Adverse Events**

- **Penile pain during injection(%):**
  - CL: 13
  - AH: 24
  - Moxisylyte: 15

- **Penile pain during erection(%):**
  - CL: 17
  - AH: 24
  - Alprostadil*: 17
  - Moxisylyte: 3

- **Penile pain after erection(%):**
  - CL: 7
  - AH: 19
  - Alprostadil*: 7
  - Moxisylyte: 0

- **Bleeding(%):**
  - CL: 3
  - AH: 15
  - Alprostadil: 3
  - Moxisylyte: 3

- **Erection > 2 hours:**
  - CL: 5
  - AH: 4
  - Alprostadil: 5
  - Moxisylyte: 0

- *(p<0.05)*
### 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.

### 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

### 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)

### Outcomes

- **Erectile response outcomes included:**
  - Patient satisfaction “with the sexual experience” on a scale of 0-10;
  - Partner satisfaction “with the sexual experience;”
  - 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).**

### Drugs and Doses

- **(1) Alprostadil 1.5µg + Papaverine 4.4mg + Phentolamine 0.15mg** (Trimex)
- **(2) External vacuum device (Osbon ErecAid)**

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Soderdahl (1997)</td>
<td>(1) Alprostadil 1.5µg + Papaverine 4.4mg + Phentolamine 0.15mg (Trimex) (2) External vacuum device (Osbon ErecAid)</td>
<td>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)</td>
<td>Inclusions: Previously untreated organic impotence; stable sexual partnership; Exclusions: 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; 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</td>
<td>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&lt;0.05) Partner satisfaction: Injection 6.5 Vacuum 5.1 (p&lt;0.05) Patient preference(%): Injection 57 Vacuum 27 Both 14 None 2 Partner preference(%): Injection 50 Vacuum 27 Both 14 Neither 9</td>
<td>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.</td>
</tr>
</tbody>
</table>
C. Abstracts

<table>
<thead>
<tr>
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<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 5 µg or 10 µg; or Transurethral Alprostadil 500 µg or 1000 µg.</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 5 µg vs. Transurethral 500 µg Injection * 2.8 Transurethral 1.5 Comparison 2: Injection 10 µg vs. Transurethral 1000 µg &quot;no statistical difference&quot; Subject satisfaction, scale from 0-5: Injection 5 µg * 3.2 Transurethral 500 µg 1.5 * (p&lt;0.01)</td>
<td>No information given.</td>
</tr>
</tbody>
</table>
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)
