



**Clinic**  
Optimizers



# Intracavernosal Penile (ICP) Injections

## Clinical Management Booklet

This information is not a recommendation nor is it intended to provide direction regarding diagnoses, treatments, or potential outcomes. Any interpretation of this information is the opinion of Clinic Optimizers and should be used by the prescriber at his/her discretion.



# Intracavernosal Penile (ICP) Injections

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**ICP injection products are commonly prescribed for:**

Treatment of erectile dysfunction in males

**Multiple strength combinations of ICP Injections are available:**

Bi-Mix 5 mL vial. Papaverine HCl 30mg/mL, Phentolamine Mesylate 1mg/mL

Super Bi-Mix: 5 mL vial. Papaverine HCl 30mg/mL, Phentolamine Mesylate 2mg/mL

Tri-Mix: 5 mL vial. Papaverine 30mg/mL, Phentolamine Mesylate 1mg/mL, Prostaglandin E1 10mcg/mL

Super Tri-Mix: 5 mL vial. Papaverine 30mg/mL, Phentolamine Mesylate 2mg/mL, Prostaglandin E1 20mcg/mL

Quad-Mix: 5 mL vial. Papaverine HCl 30mg/mL, Phentolamine Mesylate 2mg/mL, Prostaglandin E1 20mcg/mL, Atropine Sulfate 200mcg/mL

Super Quadmix: 5 mL vial. Papaverine HCl 30mg/mL, Phentolamine Mesylate 4mg/mL, Prostaglandin E1 40mcg/mL, Atropine Sulfate 400mcg/mL

Priapism Rx: 2mL pre-diluted Phenylephrine HCl 0.1% (1mg/mL) vials.

Starting dose: Injection of 0.05-.3 cc of reconstituted Tri-Mix, Super Tri-Mix or Quad-Mix solution (29-30 gauge ½ inch) as needed before sexual activity. Priapism rescue: If erection lasts more than 3 hours, inject phenylephrine at 0.5mL every 5 minutes up to 2mL until detumescence (soft penis) start occurring

**Pharmacologic Category:** Anti-erectile dysfunction preparation: vasodilator, prostaglandin, & alpha-adrenergic receptor antagonist.

### General Information

Tri-Mix is the most popular intracavernosal injection product with good efficacy to treat erectile dysfunction in most men.

Tri-Mix and other ICP injection formulations are administered as a penile self-injection, typically considered to be the most powerful class of anti-erectile dysfunction agents.<sup>1</sup> While the components of Tri-Mix are, on their own, indicated for a vast number of different conditions (papaverine, phentolamine, PGE1), the practice of bringing them together in

concert to treat erectile dysfunction has become commonplace in sexual medicine and is now considered to be the go-to treatment if conventional PDE5 inhibitors are contraindicated or nonresponsive.<sup>2,1</sup>

A small percentage of men who do not respond completely with Tri-Mix may be prescribed the Super Tri-Mix formula (same concentration of papaverine as regular Tri-Mix but double the concentration of phentolamine and prostaglandin E1) or the quad mixture (Quad-Mix) of phentolamine, papaverine, prostaglandin E1 and atropine. Others who may have pain associated with a Tri-Mix injection use a bi mixture (Bi-Mix) of phentolamine and papaverine. The starting injection volume is the same for every formulation (0.05 to 0.3 mls).

**1. Indications:** Tri-Mix is indicated in the treatment of erectile dysfunction in males. Tri-Mix contains three drugs from complimentary classes designed to act synergistically, mixed into a sterile injection. They are:

**Papaverine:** A drug that causes blood vessels to expand (vasodilator); it produces an erection by allowing for increased blood flow to the penis. Papaverine interacts with adenylate cyclase resulting in increased cyclic adenosine monophosphate (cAMP) production, ultimately resulting in increased erectile capacity by relaxation of penile smooth muscle <sup>3</sup>. This drug was one of the first effective therapies for erectile dysfunction administered by penile injection <sup>4</sup>. Papaverine works by inhibiting phosphodiesterase nonspecifically, there are also multiple other mechanisms by which this drug acts to improve erectile capacity <sup>5</sup>. The current body of medical literature has not established the predominant mechanism by which papaverine works. The multi-mechanistic manner by which this drug acts may be concentration dependent. Experimental data, performed in-vitro, displays papaverine acting to relax the penile arteries, the cavernosal sinusoids, and the penile veins <sup>6</sup>. Experiments carried out in dogs display papaverine's ability to decrease the resistance to arterial inflow while also increasing the resistance to venous outflow <sup>7</sup>. Papaverine's ability to decrease resistance to venous outflow has been replicated in clinical studies <sup>8</sup>. A veno-occlusive mechanism may be responsible for the aforementioned findings.

### **Biweekly intracavernous administration of papaverine for erectile dysfunction. 9**

**Participants:** 50 patients age 40 to 70 years old

**Administration:** intracavernosal injection at base of the penis

**Dosage:** 60 mg papaverine in 5 ml saline every 2 weeks

**Results:** Erection of 80% or more of normal was achieved by all but one patient, improves sexual potency

### **Medical treatment of impotence with papaverine and phentolamine intracavernosal injection. 10**

**Participants:** 20 patients age 32 to 72 years old

**Administration:** intracavernosal injection

**Dosage:** 30 mg papaverine and phentolamine 1 mg

**Results:** Response with erection in 20- 30 minutes, phentolamine and papaverine produced an erection sufficient for intercourse in 18 of the 20 subjects

### **Treatment of impotence by intrapenile injections of papaverine and phenoxybenzamine: a double blind, controlled trial. 11**

**Participants:** 39 patients age 27 to 67 years old

**Administration:** intracavernosal injection

**Dosage:** 60 mg Papaverine in 10 ml saline

**Results:** 35% full restoration of erectile capacity 65% partial restoration of erectile capacity

## Evaluating erectile dysfunction: oral sildenafil versus intracavernosal injection of papaverine. 12

**Participants:** 39 patients age 21 to 65 years old

**Administration:** intracavernosal injection

**Dosage:** 30 mg papaverine

**Results:** Papaverine improved length and circumference papaverine is effective as injection therapy for erectile dysfunction

**Phentolamine:** When injected into the penis, it induces an erection by relaxing and dilating the blood vessels of the penis, as well as by elevating cardiac output.

Phentolamine is classified as an Alpha-Adrenoceptor Antagonist. Noradrenaline effects the smooth muscle tone of the penile tissues by keeping the corpora cavernosa in a contracted state. By blocking the functional noradrenaline receptors, the Alpha-Adrenoceptor, erectile response can be achieved. Phentolamine competes with endogenous norepinephrine for the Alpha1-Adrenoceptor and Alpha2-Adrenoceptor. Phentolamine has similar binding capacities to both receptors. The current literature suggests that this is the main mechanism by which phentolamine exerts its physiological effects. Phentolamine also blocks 5-HT receptors, inducing the release of histamine from mast cells. Some studies also show that NOS activation could possibly be involved in another mechanism, inducing increased vasodilation [13,14](#).

The Alpha-Adrenoceptor Antagonist of phentolamine is considered to be complex. The non-selective receptor blocking action interacts with adrenergic nerves in a complex fashion. Phentolamine action on adrenergic nerves has not been fully established. It is thought that there might be counteracting regulation on pre-and post-junctional nerves. It is not known how the counteracting regulation might affect the efficacy of phentolamine for the treatment of erectile dysfunction.

In animal studies, penile arterial inflow resistance was decreased. This proves in vivo that the physiological response to phentolamine acts in a manner to achieve erectile response [7](#). However, phentolamine has not displayed a significant effect on the venous outflow from penile tissues in humans [7](#). The current body of literature has not established pharmacokinetics for phentolamine.

First pass metabolism effectively reduces the efficacy in the treatment of erectile dysfunction. Therefore, this drug has to be administered by injection. The half-life of phentolamine is 30 minutes, with an effect duration of 2.5 to 4 hours [15](#). After penile injection the concentration of phentolamine in serum reaches a maximum within 20 to 30 minutes. After this amount of time has passed the drug rapidly is metabolized [16](#).

Side effects of phentolamine are rare. However, it has been reported that orthostatic hypotension, tachycardia, arrhythmias and myocardial infarction, have occurred after penile injection. The mechanism to which this set of side effects occur has not been rationally deduced through scientific study. Phentolamine is usually added in combination with papaverine or vasoactive intestinal peptide to increase erectile response [17,18](#)

### **Medical treatment of impotence with papaverine and phentolamine intracavernosal injection. 19**

**Participants:** 20 patients age 32 to 72 years old

**Administration:** intracavernosal injection

**Dosage:** 30 mg papaverine and phentolamine 1 mg

**Results:** Response with erection in 20- 30 minutes, phentolamine and papaverine produced an erection sufficient for intercourse in 18 of the 20 subjects

**Prostaglandin E1 (Alprostadil):** A potent hormone-like substance that induces erection by relaxing the penis's blood vessels and dilating cavernosal arteries-dilation of the cavernosal arteries is accompanied by increased arterial inflow velocity and increased venous outflow resistance allowing for more blood into the penis and less blood out.

Prostaglandin E1 is administered intracavernosally. This drug is prescribed as a second-line treatment, after oral PDE5 inhibitors have been ineffective for treatment of erectile dysfunction [20](#). Several aspects of its effects and clinical use have been reviewed previously [21, 22](#). Currently the body of medical literature demonstrates that 40 to 70% of erectile dysfunction patients respond to treatment with prostaglandin E1. The failure to respond to prostaglandin E1 has not been established. The demonstration that prostaglandin E1 with S-nitrosoglutathione in combination is more effective than prostaglandin E1 alone may shed light on the lack of efficacy in some patients [23](#).

Medications to activate alternative relaxant pathways in addition to by prostaglandin E1 may be necessary in patients who fail to respond to prostaglandin E1. Relaxation of smooth muscle is a critical component of erectile capacity. Additional agents to work in combination with prostaglandin E1 might have significant therapeutic benefits. Prostaglandin E1 with other erectile dysfunction medications, might have advantages in the treatment of male erectile dysfunction. Compounding pharmacies formulate ICP injection medications that take advantage of multi-compound synergy. When injected into penile tissue prostaglandin E1 is readily metabolized into other erectile promoting molecules. These molecules potentiate the efficacy of prostaglandin E1. Prostaglandin E1 has been demonstrated to alter the concentrations of noradrenalin [24](#), adding a secondary mechanism of action. However, it is still believed prostaglandin E1 primarily acts directly by increasing cAMP synthesis via EP receptor interaction, increasing muscular relaxation [25](#).

Prostaglandin E1 has ubiquitous actions in controlling processes in many tissues. Known effects of prostaglandin E1 include systemic vasodilation, prevention of platelet aggregation, and ask to stimulate intestinal activity. Thus, prostaglandin E1 has very rarely been administered in a fashion to elicit a systemic response. Pharmacokinetics data is currently lacking on prostaglandin E1, the current data suggest short action duration and high rate of metabolic breakdown. After the first pass through the lungs 70% is metabolized [26](#). Because prostaglandin E1 is readily metabolized

throughout the body, penile injection effects mainly penile tissues. Furthermore, this further explains the rare circulatory side effects.

An example of a dosage combination for Tri-Mix is 10 micrograms of alprostadil, 500 micrograms of phentolamine and 15 mg of papaverine. Dosing of Tri-Mix preparations has not been standardized.

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## ICP INJECTION PROCEDURE

## ICP INJECTION PROCEDURE



*Click on the following link to watch a demonstration of Tri-Mix injection technique:*

[How to Inject Tri-Mix Video](#) (If link does not work, Google: YOUTUBE TRIMIX INJECTION DEMONSTRATION)

### Reconstitution Directions

**Step 1:** Remove the caps from the medication and bacteriostatic water vials. Wipe the tops with the alcohol swabs and let dry.

**Step 2:** Using the mixing syringe tighten the needle to the hub then pull back the plunger to bring in 5 mL of air. Insert the needle into the bacteriostatic water vial then invert the vial upside down.

**Step 3:** Push the plunger in and then draw out 5 mL of bacteriostatic water by slowly pulling the plunger back out.

**Step 4:** Remove the needle from the bacteriostatic water vial and insert it into the medication vial.

**Step 5:** Push the plunger to release the 5 mL of bacteriostatic water into the medication vial.

**Step 6:** Draw out the same volume of air that you've injected (5 mL) from the medication vial before pulling the needle out. This will keep the pressure equal within the vial. Swirl the vial around until the solution is clear.

**Step 7:** Discard the remaining bacteriostatic water and refrigerate the medication.

## Injection Directions

\*\*\*Please note that prior to inserting the syringe into the Medication vial you should always wipe the top of the vial with an alcohol swab first\*\*\*

Using your insulin syringes you should draw as follows according to your dose

If your dosage is not listed please follow your physician's instructions

Measurement in <b>Units</b> or <b>mL</b> with an insulin syringe	Measurement in <b>Units</b> or <b>mL</b> with an insulin syringe	Measurement in <b>Units</b> or <b>mL</b> with an insulin syringe
10 Units <b>or</b> 0.10 mL	30 Units <b>or</b> 0.30 mL	50 Units <b>or</b> 0.50 mL
20 Units <b>or</b> 0.20 mL	40 Units <b>or</b> 0.40 mL	60 Units <b>or</b> 0.60 mL

### Performing the Injection

Your nurse practitioner or nurse will review the instructions below with you. Generally, the training takes 1-2 office visits. Please be aware that each visit may take up to 1 hour so you should plan your schedule on the day of your appointment. When you are at home and on your own, use this written information to help you the first few times you perform the injection.

### Storing Your Medication

The medication will be delivered directly to your home from the compounding pharmacy after your second training visit. Store the medication in the refrigerator and keep it away from light. This can keep the medication good for up to 90 days. Don't use the medication if it:

- ~ Has particles or is cloudy.
- ~ Has expired according to the date on the label.

### Preparing the Injection

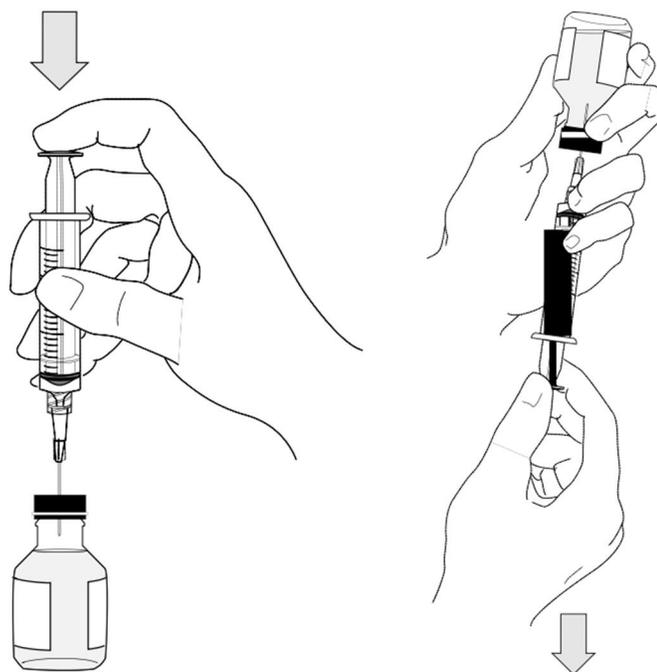
1. Prepare a clean surface on which you can place the supplies you will need.
2. Assemble your supplies:
  - ~ Medication vial
  - ~ Syringe
  - ~ Alcohol swabs
  - ~ Sharps container. You can use an empty detergent or bleach bottle with a cap, or a metal coffee can with a plastic top.

3. Take the medication out of the refrigerator.
4. Wash your hands well with soap and water.

### Drawing -up the Medication from the Vial

1. Take the tab off the vial if you are using it for the first time and throw the tab away. Open an alcohol swab and wipe the rubber stopper on the top of the vial. You must always wipe the rubber stopper with alcohol before you insert the needle to remove any bacteria.
2. Take the syringe out of its package.
3. Remove the cap from the needle. Be very careful not to let anything touch the needle. If anything touches the needle, you must throw the needle away in the sharps container and use a new one. This is because it will no longer be sterile.
4. First, pull the plunger of the syringe back past the dose you were told to inject. Next, push the plunger back up in the syringe until the top of the black tip is at the dose you were told to inject. Hold the syringe in your hand like you hold a pen or dart. Hold the syringe close to the needle with your thumb, index (first) and middle (second) fingers. This will keep the needle from bending as you insert it into the rubber stopper.
5. Insert the needle through the circle in the center of the rubber stopper on the vial. Push the plunger down and inject the air into the vial (see Figure 1). You do this because the medication is stored in a vial that is pressurized. You must replace the amount of medication you remove from the vial with air.

6. Turn the vial and syringe upside down (see Figure 2). Hold the syringe with the hand you use to write with and the vial with your other hand. Be careful not to let go of the vial or the needle will bend. Make sure the tip of the needle is in the medication. Rotate the syringe so you are looking at the numbers and lines on the syringe.

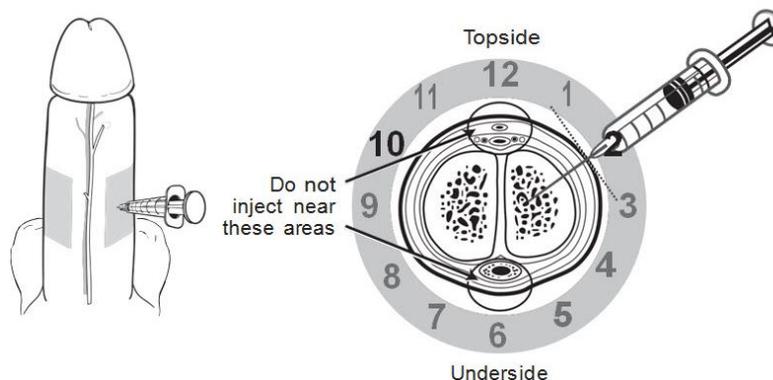


**Figure 1:** Injecting air into the vial **Figure 2:** Withdrawing the medication

7. Pull the plunger down past the dose we have prescribed. This will help remove any air bubbles. Slowly push the plunger up to the dose prescribed. Check the amount of medication in the syringe to make sure it is the correct dose.
8. Once again, check for air bubbles. If air bubbles are present, pull more medication into the syringe.
9. They will go to the top. Slowly push the air bubbles and the extra medication back into the vial. Look at the syringe again to make sure that you have the right amount of medication.
10. When you have the correct amount, pull the needle out of the vial. Then place the cap back on the syringe without touching or bending the needle. If you touch or bend the needle, you will need to discard the syringe and start at step 2. When you place the cap back on the needle, make sure you don't push the plunger by accident. This will push the medication into the cap and result in the wrong amount when it's time to inject yourself.

### Choosing an Injection Site

You must inject into a specific area of your penis. This is so you do not injure nerves, arteries, or veins. Do not inject straight down on the top or the bottom of the penis. Imagine that the penis is divided in 2 parts. The first part is from the area closest to the body to the middle of the penis. The second part is from the middle of the penis to the head of the penis. You will give the injection right behind the middle line at the 10 o'clock (left side) or the 2 o'clock (right side) position (see Figure 3). To prevent trauma to your penile tissue, always change sides of the penis each time you inject the medication (right side then the left side). Keep a record each time so you do not forget. Do not inject into any vein you can see or feel because it could cause large bruise on your penis.



Choosing an injection site

### Injecting the Medication

1. Grasp the head of your penis, not the skin. If you are not circumcised, pull your foreskin back before grasping the head of your penis. Pull your penis straight out.
2. Locate the area to be injected (right behind the middle of your penis). Wipe it with an alcohol swab. Let go of the head of your penis and pick up the syringe with 2 hands.
3. Remove the cap covering the needle. Look at the syringe to make sure the dose is correct and you haven't pushed any medication out by accident. Hold the syringe between your thumb, index and middle fingers like a pen or a dart. Do not place your index finger or thumb on the plunger until the needle is all the way in the skin.
4. Once again, grasp the head of your penis and pull it straight out. You must keep tension on your penis; do not twist it since this could lead to injecting the wrong area.
5. Touch the needle to the skin and quickly slide it into the shaft of your penis. Remember to avoid any veins. Make sure to insert the needle at a slight angle (as shown in the Figure above)
6. Move your finger so that your index (pointer) finger or your thumb can push in the plunger.
7. Quickly push down on the plunger to inject the medication into the shaft of your penis. Be careful not to pull the syringe out as you are injecting the medication.
8. Quickly remove the needle after you have injected all the medication. Pull it straight out. Do not use a twisting or jerking motion because this may cause bruising. Apply pressure for 2 to 3 minutes with your thumb on the injection site and your index finger on the opposite side of your penis. If you are taking a blood thinner or aspirin, hold the pressure for 5 minutes.
9. Place the syringe in the sharps container.



## **ICP Injections**

**Practical Tips, Questions and Answers**

## ICP Injection

### Practical Tips, Questions and Answers

#### TRI-MIX INJECTION (PAPAVERINE, PHENTOLAMINE, AND ALPROSTADIL)

**Pharmacologic Category:** Anti-erectile dysfunction agent

#### What is this medicine used for?

Treatment of erectile dysfunction. Tri-Mix contains three drugs mixed in a sterile injection. They are:

- 1.) Papaverine:** A drug that causes blood vessels to expand (vasodilator): it produces an erection by increasing blood flow to the penis.
- 2.) Phentolamine:** When injected into the penis, it produces an erection by increasing blood flow to the penis.
- 3.) Prostaglandin E-1:** A potent hormone-like substance that can control blood pressure, helping produce erections.

#### Reasons not to take this medicine:

Do not take this medicine with any of the following medications: hypersensitivity or allergy to any component of this formulation; conditions predisposing you to priapism (painful erection lasting 4 hours or more): sickle cell anemia, multiple myeloma or leukemia; anatomical deformation of the penis or with penile implants; direction by your physician that sexual activity is inadvisable or contraindicated.

#### Key warnings before taking this medicine?

Tell your doctor if you have a condition or are taking a medicine that interferes with blood clotting.

#### What are the precautions when taking this medicine?

Give your health care provider a list of all the medicines, herbs, non-prescription drugs, or dietary supplements you use. Some items may interact with your medicine.

#### How is it best taken?

Ideally, the injection should be administered just prior to foreplay. To prevent bruising, apply firm pressure to the injection site for 5 minutes after injection. It is administered via intracavernosal injections and should produce an erection in 5 to 20 minutes and can be expected to last up to one hour. Do not use Tri-Mix Injection more than 2-3 times a week due to increased risk of fibrosis; use at least 24 hours apart. There is a possibility of needle breakage with use of Tri-Mix (or Bi-

Mix, Quad-Mix, etc) injection: you should pay careful attention to your doctor's instructions and handle syringe and needle properly. If the needle breaks during injection, you should promptly contact your doctor.

### **What do I do if I miss a dose?**

Do not take double or extra doses. This medicine should only be taken 5 to 20 minutes before sexual foreplay.

### **What are some possible side effects of this medicine?**

Mild to moderate pain during injection; painful sensation with erection; small amount of bleeding at the injection site. Call your healthcare provider if you notice any redness, lumps, swelling, tenderness or curvature of the erect penis. If you experience an erection lasting more than 2 hours, you may take 2 - 4 pseudoephedrine 30 mg by mouth once and apply an ice pack. If your erection does not go away within the next hour, seek professional help immediately. Erections that last more than 6 hours can cause serious damage to the penile tissue.

### **How should I store this medicine?**

Once reconstituted keep this medicine in a refrigerator between 35°F to 46°F (2°C - 8°C). Keep all medicine out of the reach of children. Throw away any unused medicine after the expiration date. Do not flush unused medications or pour down a sink or drain.

**General statements:** Do not share or take any one else's medicine. Talk with your healthcare provider before starting any new medicine, including over-the-counter, natural products, or vitamins. This medication was compounded specifically for you. This patient information summarizes the most important information about your medication; if you would like more information, talk with your doctor.

Tri-Mix is injected directly into the side of the penis through a fine-gauge insulin-style needle in very small amounts (0.1-0.5cc) that increase blood flow to the penis. It results in strong and lasting erections. The main potential side effects are hematomas (bruising), fibrosis if used too frequently and on the same injection site, pain, and dangerously long-lasting erections (priapism).

Compounding pharmacies sell two types of Tri-Mix formulations: Freeze dried (powder to be mixed later with water) or pre-mixed vials. Pre-mixed vials need to be shipped with cold gel packs to protect them from heat. Refrigeration is required for reconstituted vials. Reconstituted product can also be frozen. Freeze dried (unconstituted) vials can be kept in a cool place away from heat.

It is extremely important to remember never to use Viagra, Cialis, or Levitra before or at the same time as you use Tri-Mix. This is a dangerous combination that can increase the risk of priapism. Be particularly careful with Cialis since it can stay in your blood stream for a longer time.

Most men who use Tri-Mix like its efficacy. Most of these men did not respond well nor had too many side effects to oral agents like Viagra or Cialis like flushing, sinus congestion, headaches, heartburn, and back ache.

A small percentage of men who do not respond completely with Tri-Mix may be prescribed the Super Tri-Mix formula (same concentration of papaverine as regular Tri-Mix but double the concentration of phentolamine and prostaglandin E1) or the quad mixture (Quad-Mix) of phentolamine, papaverine, prostaglandin E1 and atropine. Others who may have pain associated with a Tri-Mix injection use a bi mixture (Bi-Mix) of phentolamine and papaverine. Bi-Mix is often preferred by men who travel frequently since it does not require refrigeration although it is recommended to store in fridge when not traveling.

A single agent FDA approved drug that only has Prostaglandin E1 can be compounded generically or is also dispensed as injectable alprostadil either as Caverject Impulse® or Edex®. These two brand products are not as effective as Tri-Mix but may be covered by some insurance companies. Their copay may be higher than paying for Tri-Mix, though. The injection volume is also 10 times larger than Tri-Mix.

## **QUESTIONS AND ANSWERS:**

(Courtesy of USCF Dept. of Urology- San Francisco, CA, with edits)

### **POST PROSTATIC SURGERY**

Q1. After a nerve sparing Prostatectomy, will injections help recovery of my natural erections?

A1. Yes, if your nerves were spared, the use of injections, which stimulate the flow of blood to the penis, may help the recovery of your natural erections.

Q2. What is the optimal time after prostate surgery to begin injection therapy?

A2. As soon as the patient recovers from surgery and feels OK to start a sexual relationship again, usually 4 to 12 weeks after surgery.

Q3. Will injections work on men with non-nerve sparing prostatectomies?

A3. Yes. Injections work independently of the nerves

### **POST-RADIATION**

Q4. Are there different recommendations for treating erectile dysfunction with injections for erectile dysfunction resulting from radiation therapy?

A4. There is no difference

### **ICP INJECTION MEDICATIONS AND MECHANISM**

Q5. It seems that there are several different medications suitable for injections. What are they and what are the trade-offs?

A5. Each of these medications will work to help you achieve an erection. You should always consult your physician to discuss which is best for you. Some of the medicines currently in use include the following:

1. **Papaverine** is available at a low cost and is stable at room temperature but is less effective than the other medications and may have a higher tendency to cause scarring (fibrosis).
2. **Papaverine plus phentolamine (Bi-Mix)** is more potent than papaverine alone but with the same potential side effects such as priapism and scar tissue formation. It can be exposed to room temperature if needed for travel but it is
3. **Alprostadil** rarely causes priapism but with its use pain is more common. (Alprostadil is also known as prostaglandinE-1 or PGE-1, in powdered form it may be called by brand names Caverject or Edex.)
4. **Papaverine plus phentolamine plus Alprostadil (Tri-Mix)** is more potent than Bi-Mix but requires refrigeration and has the same side effects as Papaverine and Alprostadil.

Q6. How do these medications work to produce an erection?

A6. These drugs create an erection by relaxing the smooth muscles and widening the blood vessels in the penis. They also may enhance the effect of nitric oxide on erections. They are not dependent on sexual stimulation although masturbation right after injecting is recommended.

Q7. Are there long-term side effects to the use of injections? What are they?

A7. One possible side effect is the development of curvature in the erect penis, which can be painful and interfere with intercourse. This is called Peyronie's Disease. It is caused by a buildup of plaque or scar tissue inside the penis in the lining of the corpora cavernosa. These are the two sponge-like cylinders running the length of the penis into which the medication is injected. It is relatively rare and can be treated. You can minimize the risk of getting Peyronie's by learning to inject correctly. This is not difficult.

Q8. Are there medical conditions that preclude the use of injections?

A8. Yes.

1. Severe scarring of the penis.
2. Allergy to any of the 3 medications.
3. Active infection or sores on the penis.

Note: Blood thinners such as aspirin and Coumadin can increase bleeding. Men may use injection therapy when taking these medications IF they compress the injection site for at least 7 minutes. However, higher incidence of bruising may occur in these patients. Bruising disappears after a few days.

## ERECTIONS FROM INJECTIONS

Q9. What percentage of men will get a useful erection from an injection? Do injections work for everyone?

A9. If the medication is properly dosed (this is done by your physician) and properly injected, a useful erection should occur in at least 80% of men.

Q10. Does the medication continue to work indefinitely or is a tolerance created requiring increasing dosage?

A10. Tolerance is not common although some long term users (5+ years) may need to increase dose by 10-20 %.

Q11. How long will the erections last?

A11. This depends on a number of factors including: one's general health, current physical status, whether the proper dosage was properly injected and the presence of other stimulation. Erections generally appear in 5 to 10 minutes and on average last approximately 30 minutes.

Q12. Can injections be used with vacuum erection devices?

A12. DO NOT use a vacuum erection device after injecting! Serious bleeding can result. There may be exceptions. Please consult your doctor.

Q13. My medication requires refrigeration. How long can it be left un-refrigerated?

A13. Three hours. You can buy a gel pack cooler like the one shown in page 27. The Bi-Mix formulation has less strict refrigeration requirements.

Q14. If I am traveling, are there medications that don't require refrigeration that I can use in place of my regular medication?

A14. If your standard medication is Alprostadil (Prostaglandin), then Caverject or Edex can be used. These are mixed from a powder at the time of use. Papaverine + phentolamine (Bi-Mix) doesn't need refrigeration. Tri-Mix needs refrigeration after reconstitution. You can also order freeze dried Tri-Mix and reconstitute it when you get to your destination. Ensure that you have refrigeration there. Please see a suggested travel cooler shown at the end of this document.

## PRIAPISM

Q15. What is the definition of priapism?

A15. It is a prolonged erection. This is an easily managed but is a potentially serious complication. If ignored and if frequent, it may result in severe pain and complete impotence necessitating placement of a penile prosthesis. Therefore, it is very important that if you develop a full erection lasting for more than 3 hours, you should call your doctor at once or go to the emergency room. Some doctors provide you with a prescription of 2mL pre-diluted Phenylephrine HCl 0.1% (1mg/mL) vials that you may obtain with your first prescription of Tri-Mix from a compounding pharmacy. Typical protocol is to inject 0.5mL every 5 minutes up to 2mL until detumescence (soft penis) starts.

Q16. I've heard that Sudafed and Benadryl as well as Terbutaline can reduce a prolonged erection. When should these be used?

A16. Yes, they can be effective. They should be taken if the erection lasts more than 2 hours. Some men chew them for faster response. If it is still a problem after 4 hours call your doctor, follow his/her rescue protocol (see answer 15 above) or go to the emergency room.

Sudafed (pseudoephedrine) is a decongestant available without a prescription but behind the counter, meaning that you have to ask the pharmacist to get it for you. The pharmacist will ask for your identification since this drug is known to be used in the manufacture of illegal methamphetamine, so the government keeps track of frequent users. Do not use other versions of Sudafed that are available since they do not have pseudoephedrine. Chew on a 30 or 60 mg tablet with water if erection has lasted more than 3 hours. Effects should start to be noticed within 30 minutes. Be aware that this drug will disrupt your sleep or may keep you awake for hours. Having sleep aids at hand can help if you are taking Sudafed at night time.

Terbutaline is used to treat wheezing and shortness of breath from lung problems (e.g., asthma, chronic obstructive pulmonary disease, bronchitis and emphysema). Terbutaline is a bronchodilator (beta-2 receptor agonist) that works by opening breathing passages to make breathing easier. The dose is 10mg once, then take another 5mg-10mg 15 minutes after the first dose only if needed. If you have been prescribed Tri-Mix or any other ED injection product and are concerned about priapism you may request a prescription for Terbutaline to have on hand.

Q17. Can I use an ice pack to reduce an erection? Where and how should it be applied?

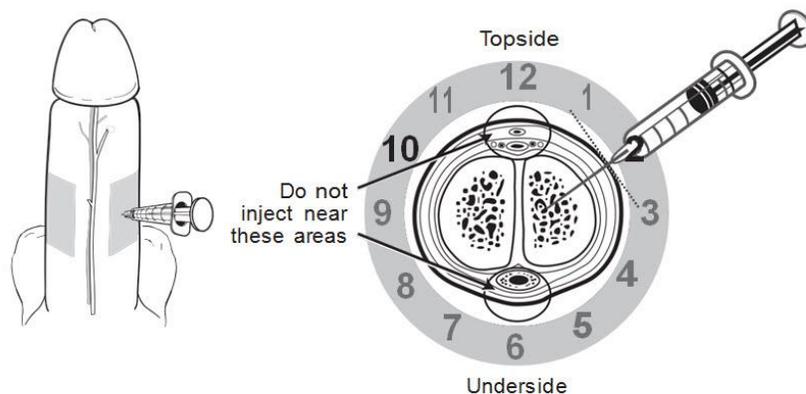
A17. Yes, on the penis or inner part of thighs. (A cold shower also works.) Again, if it is still a problem after 4 hours call your doctor or go to the emergency room.

## INJECTION MECHANICS

Q18. When filling the syringe, I have heard that that the plunger should be pulled down to the 1.0 cc mark before pushing the needle through the rubber stopper. Once the needle is pushed through

the rubber stopper, the plunger should be pressed on, pushing the air into the ampoule before withdrawing the medication. Is there an advantage to this procedure?

A18. It makes withdrawing the medication easier.



Choosing an injection site

### Correct Place to Inject

Q 19. Where in the penis do I want the medication to go? What structures am I aiming for and which do I want to avoid?

A19. After cleaning with alcohol swab, insert needle into side of penis and inject medication. See figures above and watch this video:

[How to Inject Tri-Mix Video](#) (If link does not work, Google: YOUTUBE TRIMIX INJECTION DEMONSTRATION )

Alternate between injecting at the 3 and 9 o'clock positions. You will be injecting into the corpus cavernosum (erectile bodies). When choosing an injection site, avoid any area where a blood vessel is clearly visible.

Q20. Besides the 3 and 9 o'clock positions, I've also been told that I can inject at 2, 4, 8 and 10 o'clock positions. Does it matter?

A20. 2, 4, 8, and 10 are all OK, but 3 and 9 are the best.

Q21. What should I feel when I inject? Will it hurt? Should I feel resistance? Can I feel if the needle is in too deep or too shallow?

A21. As there are few nerve endings for pain in this area, there will probably be just a slight momentary discomfort. The needle should be pushed firmly until it is fully in the penis, slight

resistance may be felt. Very small syringes of 29 to 30 gauge, ½ inch are used and they usually do not cause discomfort.

An auto-injector may reduce even further this momentary pain. Some men prefer using them but be aware they are not covered by insurance.

Q22. Are there any cues you can give me to tell when I'm in the right place? Sometimes I feel more resistance to the plunger than other times; when that happens, the injection usually fails. Why? What should I do?

A22. The amount of resistance to pushing the plunger is one of the best indicators of good needle placement. If a lot of resistance is felt then the needle may be in too far or not far enough. Pull the needle back a little or push it in further. If that does not work withdraw the needle and reinsert it in another suggested place. The plunger should depress quite easily. Your doctor can demonstrate. Do not inject if the resistance is strong.

Q23. If I don't get any response to an injection can I follow up with another injection maybe to a different side of the penis and perhaps using a smaller dose?

A23. No, the first injection may have punctured the urethra or other tissue. A second injection may cause more bleeding in the wrong area. The next time you inject (on another day) do it on the other side of the penis.

Q24. I'm bothered by the pain of the injection, are there topical anesthetics that I can use?

A24. Yes, any local anesthetic such as xylocaine jelly or cream will help. EMLA, a combination of 2.5% lidocaine and 2.5% prilocaine, is available with a prescription. ELA-Max, 4% or 5% lidocaine is available over the counter, without a prescription.

Q25. Are there thinner needles available that could be used to reduce discomfort?

A25. This is not recommended. Needle breakage has been reported with 31 gauge needles and smaller. (See following question on auto injectors.)

Q26. What's an **autoinjector** and how might it help me?

A26. An auto-injector is a spring-loaded device, which inserts the needle into the penis very quickly, minimizing the discomfort and psychological hesitancy. It comes in two forms, a simple non-prescription device designed to insert the needle for you and a prescription-required device that also depresses the plunger for you. You can check with your local drug store to obtain the simple auto-injector (no prescription required).

Moreover, many men prefer the autoinjector that does not inject the medications for them because they maintain the necessary feel to know that they have injected in the right place and to the right depth (The patient still pushes the plunger, there is no pain associated with this.) If the plunger does not push easily, as happens on occasion, withdraw the needle a little and try the plunger

again. If it is still difficult to push the plunger then use the autoinjector in a different location in the penis.

Many men are happy using the autoinjector. Check with your local drug store to obtain one. Some men have personal experience with the Becton Dickinson ~~%~~ject-Ease+ automatic injector, but there are other brands available. They are not very expensive. Here is another popular autoinjector: [Owen Mumford Autoject 2 Fixed Needle w/ External Indicator - AJ1310](#)

**Auto-Injection Technique.** The medication is drawn into the auto- injector. The side of the penis is cleaned with an alcohol swab and the injector placed against the penis. Pressing a button then activates the injector and the needle is automatically inserted.



Auto-Injection Technique. The medication is drawn into the auto-injector. The side of the penis is cleaned with an alcohol swab and the injector placed against the penis. Pressing a button then activates the injector and the needle is automatically inserted.

Q27. Can I use 'needle-less' injections systems like are being used by diabetics?

A27. No, they only place medications into the skin. The medication needs to go in to the deeper tissue (corpora cavernosa).

Q28. At what angle should the needle enter the penis? Should it be 90 degrees or a shallower angle to stay away from the urethra?

A28. The angle of injection can be defined in two different mutually independent ways. One way is as seen from above and the other way is as seen in a ~~%~~ront view.+Ninety degrees should be used in every view.

Injecting the needle at 90 degrees will ensure that you will not puncture the urethra. A shallow injection should not be used because the medication will not get into the corpora cavernosa, and not be effective.

Q29. Sometimes I see a tiny amount of blood from the injection site just when the needle is withdrawn and sometimes I don't. Why? Is it a problem either way?

A29. It depends on whether or not you hit a small blood vessel. It is not a problem.

Q30. What's the best way to hold the penis for the injections? Should the penis be pulled to maximum extension? Should I pull just the outer layer or the whole penis?

A30. If you need to, you should pull the whole penis. But some men find it best to lay the penis along one leg while injecting, without pulling.

Q31. Is it important to apply pressure to the injection site for a full 5 minutes after injections? Aren't a few minutes enough?

A31. Five minutes is best. On the needle site, using an alcohol swab. Immediately apply pressure to the penis with the thumb and index finger for 5 minutes, or longer if there is still bleeding.

Q32. Should I vary the injection site? What is the best way to do that?

A32. The places for injection are limited by the anatomy of the penis and you must adhere to these. Changing injection sites from left to right and back again is recommended.

Q33. Is it important to get all the bubbles, even the littlest, out of the syringe before injection?

A33. Removing those as small as poppy seeds is not necessary.

#### **DOSAGE, etc.**

Q34. How is the correct dosage determined? How do I know when I have the right dose?

A34. Dose consists of both the strength of the medication and the amount used. With the appropriate strength and amount of drug as determined by a physician (usually less than 0.5 cc), erections usually occur in 5 to 10 minutes, last for approximately 30 minutes to an hour, and become more rigid if sexual stimulation occurs.

Q35. Is sexual stimulation required for an erection? Can I use less medication if I have more stimulation?

A35. Stimulation is not required but may speed things up a bit. You may be able to use less medication with stimulation. Masturbating right after applying pressure on the injection site may also help speed up the effect and better distribute the product throughout your penis.

Q36. Sometimes a dose that has worked fine before, produces no erection. I'm sure I injected in the right place. What happened?

A36. You were probably in the wrong place or too deep or too shallow, or the medication had expired (lost its effectiveness).

Q37. My instructions say not to inject more than twice a week. What's the reason for not injecting every day, for example?

A37. Injecting into the penis frequently may cause scarring.

Q38. Does the medication lose potency over time even if stored correctly?

A38. Yes, after about six months the medication will be less effective.

Q39. Will I develop a tolerance over time requiring an increasing dose?

A39. This occurs infrequently but if it does, your physician may have to readjust the dosage of medication.

## POTENTIAL PROBLEMS

Q40. What, if any lasting damage can be done to the penis by the wrong injection technique? Can just one injection if done incorrectly cause permanent damage?

A40. Yes, although it is rare, scarring can occur (Peyronie's disease). If a patient injects too much medication it could cause priapism and damage to the erectile tissue. Not compressing the injection site after injection may cause internal bleeding and scar tissue.

Q41. After an injection I've seen blood coming from the urethra. What happened? What should I do immediately if this happens?

A41. You have punctured the urethra. Grab the whole penis and squeeze for 5-7 minutes.

Q42. What happens if I accidentally hit a large blood vessel? What should I do?

A42. If bleeding continues after applying pressure, abstain from intercourse until bleeding stops. Continue to apply firm pressure until bleeding stops.

Q43. Do infections ever develop from injections? How common is this?

A43. This happens very rarely.

Q44. Does the injection site make me more susceptible for contracting a sexually transmitted disease?

A44. Possibly, but not likely. If in doubt, put on a condom.

Q45. Can injections be used while taking Viagra orally? If so, can a lower dose be used?

A45. You should not inject and take Viagra at the same time. Using both treatments together causes an increased possibility of priapism. (Consider alternating using Viagra and injections.)

Q46. After using injections for a while my erections have developed a curvature. What's happening?

A46. The injections may have caused some scar tissue to have formed. This condition is called Peyronie's disease. Talk to your doctor about causes and treatment.

Q47. Does this curvature develop for all men using injections?

A47. No, only 3-8 percent of men.

Q48. Can this problem be the result of improper injection technique?

A48. Yes. The patient must make sure that he maintains pressure on the injection site for 5 minutes to stop bleeding; including possible internal bleeding that will not be seen. Also, attention must be paid to the doctor's instructions on where to inject, the alternation of injection sites, and the frequency of injections. Ensure that you spread the product well in your penis via masturbating in a milking-fashion to help distribute it and avoid localized fibrosis in injection site.

Q49. It is difficult for me to inject on both sides, because I am right handed I have difficulty injecting on one side. I inject less than 100 times a year. Is it crucial to inject both sides?

A49. It is better if you can inject both sides. You can go wrong with alternating sides even if you only use injections monthly. However, you do not need to change sides if injections are used less than twice a week.

Q50. Can just one injection cause Peyronie's disease?

A50. If too much medication is injected or if the medication is injected incorrectly it is possible but not likely.

Q51. Can men that develop curvature continue to safely use injections?

A51. If it is a mild curvature.

Q52. Are there medications that can be helpful? (to treat curvature of the penis?)

A52. Colchicine may be helpful in the early phases of Peyronie's disease.

Q53. Can surgery be useful?

A53. Yes, but only when the condition has stabilized, and after non-surgical treatments have failed.

#### ACCESSORIES:

For men who want to carry pre-loaded TRI-MIX, this carrying case is good. It prevents unintentional pushing of the plunger.

"The Wright Prefilled Syringe Case makes transportation of prefilled syringes as simple as carrying a fountain pen. Designed to fit in a pocket or purse the Wright Prefilled Syringe case holds most E-Z JECT B-D PharmaPlast and TERUMO syringes (not compatible with Monoject syringes). The interior is designed to safely hold the syringe plunger in your preset position with the approximate dosage. Constructed of impact resistant polypropylene the kit comes with one black and one white case. This is the safest way to carry prefilled syringes. Snaps shut. Fits popular syringes. Carry in pocket or purse. Contains a black and white case. Syringe not included."

## Wright Prefilled Syringe Carrying Case - Pack of 2

### Travel Case

This travel case and cooler is very practical for traveling with Tri-Mix and other injectables that



require refrigeration

- The Medicoool Insulin Protector Case keeps insulin cool for up to 16 hours.
- Comes with two refreezeable cooler packs. Use one while you freeze the other.
- Carries up to two bottles of any brand insulin
- Provides pockets for syringes and alcohol swabs



Buy: <http://smile.amazon.com/qp/product/B...prd ttl sol 18>

## HOW TO PREVENT PRIAPISM CAUSED BY TRI-MIX

**What is priapism:**

Priapism is an involuntary erection which lasts more than 4 hours and is unrelieved by ejaculation. This condition is a true urological emergency and early treatment allows the best chance for functional recovery.

### How to prevent priapism when taking Tri-Mix or other penile injection therapies (ICP):

- NEVER take Tri-Mix or any ICP injection within same 24hr period as Viagra/Cialis/Levitra or other ED meds.
- Start LOW and go SLOW with your dose. Never start higher than 0.05-0.12ml (5-12 units on syringe) for the FIRST injection. Then gradually increase from there for optimal results.

### If priapism occurs:

- **Apply ice to perineum/scrotal area-** You can use a frozen bag of fruit or vegetables if an ice pack is not available.
- **Walk/jog upstairs-** This can help redirect blood flow from the penis.

### Over-the counter medications to take:

- **Sudafed** (pseudoephedrine) is a decongestant available without a prescription but behind the counter, meaning that you have to ask the pharmacist to get it for you. The pharmacist will ask for your identification since this drug is known to be used in the manufacture of illegal methamphetamine, so the government keeps track of frequent users. Do not use other versions of Sudafed that are available since they do not have pseudoephedrine. Chew on a 30 or 60 mg tablet with water if erection has lasted more than 3 hours. Effects should start to be noticed within 30 minutes. Be aware that this drug will disrupt your sleep or may keep you awake for hours. Having sleep aids at hand can help if you are taking Sudafed at night time. 60mg-150mg orally. Note: Do not use Sudafed if you have used an MAO inhibitor such as furazolidone (Furoxone), isocarboxazid (Marplan), phenelzine (Nardil), rasagiline (Azilect), selegiline (Eldepryl, Emsam, Zelapar), or tranylcypromine (Parnate) in the last 14 days.
- **Benadryl** - chew 25mg-50mg orally
- **Amyl Nitrate:** Poppers is another name Amyl Nitrate and is sold in head shops, sex toy shops or smoke shops as an air freshener. It is also available online. Many guys who are very experienced with ICP injections use Amyl Nitrate to treat priapism when it occurs. It is very safe if used properly. The possible side effects include headaches, decreased blood pressure and potential loss of arousal after a few minutes. It should be used with caution in men with high risk of hypotension (low blood pressure). It should not be used with ED drugs like Viagra since this may cause a sudden drop in blood pressure

### *How to use amyl nitrate to treat priapism:*

Usually sold as ~~poppers~~, amyl nitrate usually comes in a bottle.. Inhale over 3 seconds, wait for at least 10 minutes and inhale again once if erection does not start decreasing. Headaches and flushing are common.

### **Prescription medications**

**Terbutaline-** 10mg once, then take another 5mg-10mg 15 minutes after the first dose only if needed. If you have been prescribed Tri-Mix or any other ICP injection and are concerned about priapism you may request a prescription for Terbutaline to have on hand.

**Phenylephrine:** Some physicians provide you with a prescription of 2mL pre-diluted Phenylephrine HCl 0.1% (1mg/mL) vials that you may obtain with your first prescription of Tri-Mix from a compounding pharmacy. Typical protocol is 0.5mL every 5 minutes up to 2mL until detumescence (soft penis) starts. Phenylephrine use has potential cardiovascular side-effects and it is recommended that blood pressure and pulse are monitored every 15 minutes for an hour after the injection. This is particularly important in older men with existing cardiovascular diseases.

**If these do not work and erection has been present for 4hrs and/or is painful then immediately visit the ER for treatment.**