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PATIENT GUIDE

Penile injection therapy *for erectile dysfunction*

Injecting a small dose into the side of the penis produces an erection without waiting for arousal. Alprostadil alone is FDA approved; the two, three and four drug mixes are compounded.

MIXES	INGREDIENTS	ROUTE	STATUS	SOURCES
Bi, Tri and Quad Mix	Up to four drugs	Into the penis	Compounded	24 · PMID linked

§ 01

Overview

Erectile dysfunction is common and becomes more so with age: in a survey of men aged 40 to 70, 52 percent reported minimal, moderate or complete difficulty getting or keeping an erection.[1] Tablets are where most men start and they do a great deal of good, though the American Urological Association notes that they do nothing for about four men in ten.[2] A small dose of medicine injected into the side of the penis acts on the erectile muscle itself, so it can work when the nerve signal does not arrive, and the AUA asks that every man with erectile dysfunction be told about it along with the benefits and the burdens.[3]

Four drugs are used this way: alprostadil, papaverine, phentolamine and atropine.[2] Alprostadil on its own is FDA approved for injection into the penis and is the only one of the four that is.[2 4] The three mixes on our menu, Bi Mix, Tri Mix and Quad Mix, combine two, three or four of them in one syringe; they are compounded by a pharmacy on a prescription and no combination has FDA approval. Tablets and troches are covered in our oral medicines guide (OCW WP 062), and PT 141, which acts in the brain instead, in our PT 141 guide (OCW WP 014).

94% **Of injections allowed sexual activity.** In a six month study of self injected alprostadil in 683 men, that was the share of injections after which men reported being able to have sex.[5]

1 **Of the four injected drugs is FDA approved for this use.** Alprostadil alone, as Caverject and edex. Papaverine, phentolamine and atropine are not.[2 4]

37% **Reported ache in the penis.** Across 1,861 men treated with alprostadil for up to 18 months, usually mild or moderate, against 2 percent of 294 men given placebo.[6]

4 **Hours is the line between a long erection and an emergency.** Past 4 hours an erection is classed as priapism and needs urgent care the same hour.[7]

§ 02

What these injections are

Alprostadil is a synthetic copy of prostaglandin E1, a substance the body already makes. Injected into the erectile tissue it relaxes the smooth muscle there, and it is FDA approved for treating erectile dysfunction and for helping to diagnose it, sold as Caverject, Caverject Impulse and edex.[6] [8] The other three drugs reach the same muscle by other routes: papaverine is an old smooth muscle relaxant, phentolamine blocks alpha receptors, and atropine blocks a muscarinic receptor. All three are made as injections for other purposes and none has FDA approval for erectile dysfunction. Phentolamine and atropine injections are approved for other conditions, while papaverine injection has no approved application at all, and its own label states that it is not indicated for treating impotence by injection into the penis and that such injection has caused persistent priapism needing medical and surgical treatment. [4] [9]

A mix puts two, three or four of these drugs into one solution. Because no combination has an FDA approved product behind it, a mix has to be compounded: a licensed pharmacy prepares it on a prescription written for one person, at the concentration the physician specifies.[3] Compounded medicines are not FDA approved, and the agency does not review their safety, effectiveness or quality before they are sold. [10]

THE THREE MIXES AND THE APPROVED SINGLE DRUG	
Bi Mix	Phentolamine and papaverine. Compounded; not FDA approved[10]
Tri Mix	Alprostadil, papaverine and phentolamine. Compounded; not FDA approved[3]
Quad Mix	Those three with atropine added. Compounded; not FDA approved[3]
Alprostadil alone	Prostaglandin E1, FDA approved for injection into the penis as Caverject and edex[6] [8]
Also called	Intracavernosal injection therapy, often shortened to ICI; the corpora cavernosa are the two cylinders of erectile tissue the needle enters
Where it comes from	Alprostadil as a manufactured vial or cartridge; a mix from a licensed compounding pharmacy against your own prescription[3]
How it is given	A very fine needle into the side of the shaft, in the proximal third, alternating sides; the first dose is given in the office[6] [3]

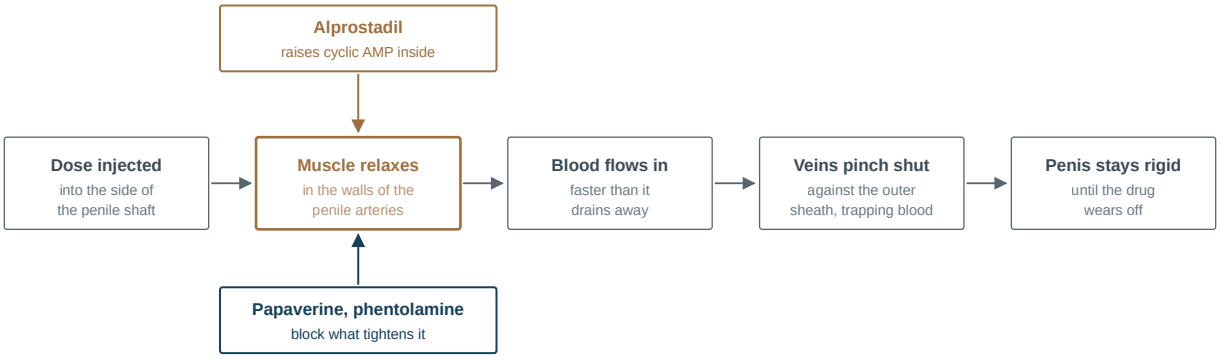
§ 03

How they work

An erection is a hydraulic event with a nerve switch. Arousal sends signals down the nerves to the penis, nitric oxide is released in the erectile tissue, and the smooth muscle in the walls of the penile arteries relaxes. Blood then flows in faster than it can drain away, the two cylinders of erectile tissue swell, and the swelling itself pinches the drainage veins shut against the tough sheath around them, so the pressure holds. A tablet works at the end of that chain and cannot start it, so a tablet does nothing without arousal.

An injected drug starts further along. It reaches the smooth muscle directly and relaxes it without waiting for a nerve signal, so it can produce an erection in a man whose nerves have been damaged by surgery or by diabetes.[6] Alprostadil does this through its own receptor, raising a messenger called cyclic AMP inside the muscle cells. Papaverine blocks the enzymes that clear away both of the messengers that keep the muscle relaxed. Phentolamine blocks the alpha receptors through which the body's own adrenaline keeps the muscle contracted. Atropine blocks a muscarinic receptor on the same tissue. [2]

Putting several of them together was meant to add their effects while keeping the dose of each one down, and the surgeons who first described the four drug mixture argued that this synergism lets a smaller total dose work.[11] Whether a mix performs better than alprostadil alone is a separate question, and one the published evidence has barely tested.



The injected drugs reach the erectile muscle directly, so the chain starts without a nerve signal. Alprostadil acts through its own receptor and raises cyclic AMP inside the smooth muscle cells, papaverine blocks the enzymes that clear away the messengers keeping the muscle relaxed, phentolamine blocks the alpha receptors through which adrenaline keeps it contracted, and atropine blocks a muscarinic receptor on the same tissue.[2] Because nothing switches the erection off when arousal fades, the dose is set in the office to produce an erection that does not run past about an hour.[6]

KEY POINT

Acting on the muscle rather than on the nerve signal lets an injection work after tablets have failed, and it also creates the main risk. The erection does not switch itself off when arousal fades; it lasts until the drug clears, so the dose is titrated in the office to produce an erection that suits intercourse and does not run past about an hour.[6 8]

§ 04

What the research shows

Alprostadil on its own has the evidence base of a licensed medicine: randomized, placebo controlled trials in several hundred men, with the results printed on its label.[5 6 8] The mixes do not. They have been used in clinics since the 1980s and the published experience with them runs to thousands of men, almost all of it in uncontrolled series rather than in trials with a comparison group. The AUA review of this literature found that more than 90 percent of the study arms came from observational designs, that most of the studies predate the validated questionnaires now used to measure erectile function, and that side effect reporting varied and rarely graded severity.[3]

What the evidence supports

Injection works for most men who try it, whichever agent is used. In the three studies behind the alprostadil approval, a dose response trial in 296 men found every dose from 2.5 to 20 micrograms better than placebo, and in the six month self injection study of 683 men, sexual activity followed 94 percent of injections, rated satisfactory by the men after 87 percent and by their partners after 86 percent.[5] The Caverject label reports an overall response of 76 percent in 153 men, no response at all to placebo, and a mean erection of 70.8 minutes.[6] Across the whole injection literature the AUA found success rates from 53.7 to 100 percent "without marked differences across medications or medication combinations", with satisfaction from 46.3 to 98.8 percent and the lowest where papaverine was used alone, averaging 53.4 percent.[3]

The mixes perform well in clinic series. The first large Bi Mix series, 100 men given papaverine with phentolamine in 1986, reported functional erections in 100 percent of those whose difficulty was neurological and 65.7 percent of those whose difficulty was arterial; four men needed treatment for an erection that would not settle.[12] In a clinic programme of 1,412 men followed over five years, most using Tri Mix, 89 percent of the Tri Mix users were able to have intercourse and the recorded priapism rate was 0.5 percent. [13] The Quad Mix series are small: 95 percent of 56 men with a venous leak obtained sustained rigid erections, and 70 percent of a second series of 94 men were still satisfied on their original dose at a mean of 20 months. [11] [14]

Stepping up through the mixes rescues men who did not respond to a simpler one. In a programme of 625 men moved through four protocols in order, 66.4 percent responded to papaverine with phentolamine; of the 210 who did not, 36 percent responded to prostaglandin E1 alone, 72.6 percent of the next 135 to the three drug mix and 59.5 percent of the final 37 to the four drug mix. All four failed in 15 men, 2.4 percent. At three years, 33.1 percent were still having intercourse with an injection and another 10.6 percent without one.[15]

It works where the nerve supply has been damaged. Injection is the second line treatment after radical prostatectomy in men who do not respond to tablets, and part of penile rehabilitation after that operation.[16] In men with a spinal cord injury, a systematic review and meta analysis of 23 studies and 713 men found successful erections in 88 percent, with 93 percent for papaverine with phentolamine and 80 percent for alprostadil, although no factor predicted who would respond. [17]

Alprostadil alone has the lowest recorded priapism rate. Averaging across study arms, the AUA found priapism in 1.8 percent of men using alprostadil as a single drug, the lowest figure for any injected agent, alongside a mean of 6.3 percent for prolonged or painful erections.[3] A survey of the world literature together with one centre's 4,577 patients over seven years put the response rate for prostaglandin E1 above 70 percent, with priapism in 0.35 percent against 6 percent for papaverine with phentolamine, and fewer scarring complications as well. [18]

What is not yet known

No trial has compared the three mixes with one another, and only one randomized study has compared a mix with alprostadil alone. In that study 180 men each received Tri Mix at one of nine ingredient combinations and, a week apart, 20 micrograms of prostaglandin E1. Blood flow, time to erection, rigidity, pain and satisfaction came out the same, and the men expressed no preference; prostaglandin E1 gave shorter erections and less priapism, and even the smallest Tri Mix doses performed as well as the largest.[19] A 2025 systematic review and meta analysis pooled nine studies, five of them randomized, and found no significant difference between single drugs and combinations in pain or fibrosis; priapism was more frequent with combinations when every study was pooled, with an odds ratio of 1.84 and a confidence interval of 1.03 to 3.20, though that difference disappeared among the randomized trials alone. Its authors give the small number of available studies as the main limitation. [20]

Nothing has been published on a four drug mix beyond those two small series, so the figures for Quad Mix rest on fewer than 200 men. No study has shown that a mix produces better erections than alprostadil alone, and both alprostadil labels state that the safety and effectiveness of combining it with other vasoactive drugs have not been established in clinical studies, that the risks of prolonged erection, priapism and low blood pressure may be increased, and that such combinations are not recommended.[6] [8] The case for a mix rests on the clinic experience and on the two things the series do suggest: less pain than alprostadil alone, and a response in some men who did not respond to a single drug. [3] [15]

THE MAIN HUMAN EVIDENCE Most of these studies had no comparison group, and they were run separately, so they cannot be compared with one another unless the study itself made the comparison.

STUDY	N	DESIGN	MAIN FINDING
Linet 1996[5]	683	Six month self injection study, alprostadil, within a three study programme	Sexual activity after 94 percent of injections; pain in 50 percent of men but after 11 percent of injections
Caverject label[6]	153	Double blind, placebo controlled crossover, then at home	Response 76 percent, no response to placebo, mean erection 70.8 minutes
edex label[8]	222	Two double blind, placebo controlled crossover phases at home	Erection sufficient for intercourse in 74 and 73 percent against 7 and 13 percent on placebo
Porst 1996[18]	4,577	Review of the world literature with one centre over 7 years	Prostaglandin E1 response above 70 percent; priapism 0.35 percent against 6 percent for Bi Mix
Sidi 1986[12]	100	Uncontrolled series, Bi Mix	Functional erections in 100 percent of neurological and 65.7 percent of arterial cases
Seyam 2005[19]	180	Randomized, Tri Mix at nine dose combinations against prostaglandin E1	No difference in flow, rigidity, pain or satisfaction; Tri Mix gave longer erections and more priapism
Baniel 2000[15]	625	Sequential protocols: Bi Mix, then alprostadil, Tri Mix, Quad Mix	Response 66.4, 36, 72.6 and 59.5 percent in turn; all four failed in 2.4 percent
Montorsi 1993[11]	56	Uncontrolled series, Quad Mix, venous leak	Sustained rigid erections in 95 percent; 11 percent had stopped by a mean of 16 months
Montorsi 1993[14]	94	Uncontrolled series, Quad Mix, arterial disease	70 percent satisfied on the original dose at a mean of 20 months; 15 percent stopped
Coombs 2012[13]	1,412	Clinic cohort over 5 years, most using Tri Mix	89 percent of Tri Mix users able to have intercourse; recorded priapism 0.5 percent
Chochina 2016[17]	713	Systematic review and meta analysis, 23 studies, spinal cord injury	Successful erections in 88 percent, 95 percent confidence interval 83 to 92
Lima 2025[20]	12 studies	Systematic review and meta analysis of single drugs against combinations	No difference in pain or fibrosis; more priapism with combinations overall, not in the randomized trials

SUMMARY

Injection into the penis is the most reliable medical treatment for erectile dysfunction and works for most men who try it, including men for whom tablets do nothing. Alprostadil alone is the form with FDA approval, randomized placebo controlled evidence and the lowest recorded rate of priapism, so it is the sensible place to begin. The mixes have forty years of clinic experience behind them, cause less pain in the published series, and bring some men to a response when a single drug did not, but their evidence is observational, nobody has compared them with each other, and the one randomized comparison with alprostadil found equal erections and more priapism.

§ 05

How these injections are given

The needle is very fine, a 29 or 30 gauge half inch needle for alprostadil, and it goes into the side of the shaft in the proximal third, away from the visible veins, with the side alternated at each use. Pressing the spot with gauze for five minutes afterwards limits bruising, which matters more if you take warfarin or heparin.[6]

The first dose is given here, not at home

Both alprostadil labels require the first injections to be given in the office by trained staff, with the dose titrated to the lowest one that works and the man staying until the erection has fully settled.[6] [8] The AUA makes the same point for every injected agent, approved or compounded: a man considering this treatment should have an in office injection test, both to find the right drug and dose and to build his confidence with the technique, and it may take more than one visit. [3] Self injection at home follows once your technique has been assessed, and the labels ask for an office visit about every three months while injections continue, with the penis examined each time. [6] [8]

Alprostadil alone

The Caverject label starts at 2.5 micrograms when the cause is vascular, psychological or mixed and at 1.25 micrograms when it is purely neurological, such as after a spinal cord injury. If the response is partial, a second dose of the same size may be given within the hour, and no more than two doses go in within 24 hours during titration. Further steps are 5 to 10 micrograms at least 24 hours apart, until the dose produces an erection suitable for intercourse that does not last longer than an hour. Doses above 60 micrograms are not recommended, and injections no more than three times a week with at least 24 hours between them.[6] The edex label gives the dose range as 1 to 40 micrograms and reports a mean dose at the end of titration of 10.7 micrograms in a study that went up to 20 micrograms and 21.9 micrograms in two that went up to 40; doses above 40 micrograms have not been studied. [8]

Bi Mix, Tri Mix and Quad Mix

No regulator has set a dose or a strength for any of the mixes, because none of them has an FDA label. The pharmacy prepares the concentration your physician prescribes, and the dose is found by titration in the office in the same careful way.[3] The AUA records that concentrations vary widely in the published literature, that ratios of 12 to 30 mg of papaverine with 10 to 20 micrograms of alprostadil and 1 mg of phentolamine per millilitre are common, and that one standard regimen is 30 mg of papaverine with 10 micrograms of alprostadil and 1 mg of phentolamine per millilitre, starting at 0.1 to 0.5 mL. [3] The randomized dose finding study used 1 mg of phentolamine with prostaglandin E1 at 2.5, 5 or 10 micrograms and papaverine at 5, 10 or 20 mg, and found no meaningful difference across those strengths. [19] The four drug series used 12.1 mg of papaverine, 10.1 micrograms of prostaglandin E1, 1.01 mg of phentolamine and 0.15 mg of atropine per millilitre, with a mean injected volume of 0.42 mL. [11] The frequency limit and the target of an erection no longer than about an hour apply to a mix as they do to alprostadil. [6]

WHAT IS SET BY A LABEL AND WHAT IS SET BY YOUR PHYSICIAN

	ALPROSTADIL ALONE	BI MIX, TRI MIX, QUAD MIX
FDA approved for this use	YES	NO
Who sets the dose	The FDA label, titrated within it[6]	Your physician; no label exists[3]
Starting dose	2.5 micrograms, or 1.25 for a purely neurological cause[6]	0.1 to 0.5 mL of a mix in the regimen the AUA describes[3]
First dose in the office	Yes, always[6]	Yes, always[3]
Target erection	Good enough for sex, under 1 hour[6]	The same target[6]
How often	No more than 3 times a week, 24 hours apart[6]	The same limit is applied[6]
Review	Office visit and examination about every 3 months[6] [8]	The same[3]

§ 06

What to expect

The office visit. The erection begins within minutes, and in the alprostadil trials it lasted a mean of 70.8 minutes per injection.[6] You stay until it has gone down completely, which is part of the point of doing the first dose here, and several visits may be needed before the drug and the dose are right. [6] [3]

The first weeks at home. Ache in the penis is the commonest complaint with alprostadil, reported at least once by 37 percent of men in the Caverject studies and usually mild or moderate.[6] The edex figures show the distribution: pain accompanied 15 percent of injections, was rated mild for 80 percent of those, moderate for 16 percent and severe for 4 percent, and it faded with time, affecting 41 percent of men in the first two months and 3 percent by months 21 to 24. [8] The mixes hurt less in the published series, which is one reason they are used: pain with injection averaged 2.0 percent across the Tri Mix arms the AUA extracted and was not reported in the Quad Mix arms, against 25.4 percent for alprostadil alone. [3]

Over months and years. Men stop this treatment more often than the response rates would suggest. Published discontinuation rates run above half, and in the clinic cohort of 1,412 men a large share had stopped by the end of the third year, some of them because natural or tablet assisted erections had come back.[13] In the four drug series, 11 and 15 percent had stopped by a mean of 16 and 20 months, while a fifth were holding a good erection on a smaller dose than they started with. [11] [14] Telling us early that something is not working, or is costing more discomfort than it is worth, gives us more to change than telling us late.

DURING TREATMENT

- An erection that lasts more than 4 hours needs urgent care that hour, not the next morning.[6] [7]
- Report any new bend, lump or firm band in the shaft, or pain that was not there before, because both alprostadil labels ask for the penis to be examined about every three months and for treatment to stop if an angle or a firm band appears.[6] [8]
- Keep to the dose agreed in the office and to the agreed frequency. Doubling up is the common route to a prolonged erection.[6] [3]
- The needle is superfine and can break, with a piece left in the penis, so handle the syringe as you were taught and tell us at once if it happens.[6] An injection also gives no protection against sexually transmitted infection, and the bleeding at the site can make transmission between partners more likely. [6] [8]

§ 07

Safety

Three risks matter with any injection into the penis: an erection that will not go down, scarring inside the shaft, and bruising or bleeding at the site. A fourth, a dosing mistake, turns the first of those from rare into likely.

AN ERECTION LASTING MORE THAN 4 HOURS IS A MEDICAL EMERGENCY

An erection of more than 4 hours is classed as priapism. The AUA and the Sexual Medicine Society of North America state that acute ischemic priapism, in which blood stops moving through the erectile tissue and turns hypoxic and acidic, is a medical emergency that can scar the tissue and leave lasting erectile dysfunction, and that everyone with it should be assessed emergently.[7] Untreated, the natural history is days to weeks of painful erections followed by permanent loss of erectile function, and how much is lost tracks how long the episode ran: in men who needed surgery, scarring and tissue death had begun as early as 12 to 24 hours and no living tissue was left by 36 hours. [7] The alprostadil labels put it in fewer words: seek immediate medical assistance for an erection that persists longer than 4 hours, because untreated priapism may damage the penis and cause permanent loss of potency. [6 8]

For an erection under 4 hours that follows an injection, the guideline's first treatment is phenylephrine injected into the erectile tissue, which produced detumescence in 71 to 93 percent of reported cases.[7] The AUA advises trying to ejaculate, then oral pseudoephedrine and an ice pack for 30 to 60 minutes; if a painful, rigid erection persists, it asks the man to be at an emergency room within 2 to 4 hours of the injection. [3] Please call us as soon as an erection passes two hours, and go to an emergency department if you cannot reach us.

Scarring inside the shaft is the risk that builds with time. The Caverject label reports penile fibrosis in 3 percent of men across its studies and in 7.8 percent in one self injection study lasting up to 18 months; the edex label reports 7.8 percent including Peyronie's disease over 24 months, with penile angulation in 7 percent of 1,065 men. Both ask for the penis to be examined about every three months and for treatment to stop if an angle or a firm band develops.[6 8] Across the wider literature the AUA found a wide range of fibrosis rates with no single drug or combination clearly worse than the others, and the proportion of men reporting it did not rise with longer follow up; it asks that any existing plaque, firm band or bend be written down before the first injection. [3] The 2025 meta analysis found fibrosis reported in only four of its twelve studies, at rates from 0.8 to 15 percent, with no difference between single drugs and combinations. [20]

Bruising and bleeding. Injection site hematoma occurred in 3 percent and ecchymosis in 2 percent of the Caverject studies, while the edex studies, which counted more carefully, recorded bleeding in 15 percent, hematoma in 5 percent and ecchymosis in 4 percent of 1,065 men, most of it attributed to faulty injection technique.[6 8] Five minutes of firm pressure after each injection is the remedy, and it matters more if you take a blood thinner. [6]

Effects beyond the penis are uncommon. Dizziness was the only systemic reaction reported by 1 percent or more of the 1,861 men in the Caverject studies, and 0.2 percent stopped because of symptomatic low blood pressure.[6] Because erectile dysfunction is itself a marker of cardiovascular risk, the Princeton IV consensus asks that a man be treated as being at risk until shown otherwise and that his fitness for sexual activity be settled before treatment starts, and the alprostadil labels say these treatments generally should not be used where sexual activity is inadvisable because of the heart. [21 6]

SIDE EFFECTS ON THE TWO ALPROSTADIL LABELS Percent of men reporting each effect. The two labels report separate studies of different length and different counting, so the columns are not a head to head comparison.[6 8]

EFFECT	CAVERJECT, 1,861 MEN TO 18 MONTHS	EDEX, 1,065 MEN TO 24 MONTHS
Penile pain	37%	29% at injection, 35% with erection
Prolonged erection, 4 to 6 hours	4%	4%
Priapism, more than 6 hours	0.4%	Under 1%
Penile fibrosis	3%, and 7.8% in one 18 month study	7.8% including Peyronie's disease
Hematoma at the site	3%	5%
Bruising at the site	2%	4%
Stopped because of a side effect	3% for pain alone	About 9%, against under 1% on placebo

WHAT THE AUA FOUND ACROSS THE PUBLISHED INJECTION STUDIES Each figure is the average of the percentages reported by the separate study arms the AUA panel extracted, with the number of arms in brackets. More than 90 percent of those arms were observational, the arms differ in length and in how severity was defined, and the men given a mix were often those a single drug had already failed, so these averages describe the pattern in the literature rather than a fair comparison between the agents.[3]

INJECTED AGENT	PAIN WITH INJECTION	FIBROSIS, NODULE OR PLAQUE	PROLONGED OR PAINFUL ERECTION	PRIAPISM
Alprostadil alone	25.4% (22)	4.9% (24)	6.3% (15)	1.8% (20)
Papaverine alone	40.3% (3)	9.9% (7)	4.9% (5)	7.1% (5)
Bi Mix	14.4% (6)	13.0% (15)	8.9% (7)	5.5% (15)
Tri Mix	2.0% (4)	4.5% (6)	2.8% (2)	3.2% (5)
Quad Mix	0% (3)	6.3% (3)	Not reported	4.8% (2)

TELL YOUR PHYSICIAN BEFORE STARTING IF ANY OF THESE APPLY

- You have sickle cell disease or sickle cell trait, multiple myeloma or leukemia, or you have ever had an erection that would not go down. Both alprostadil products are contraindicated in these conditions.[6 8 7]
- Your penis bends, has a lump or a firm band, you have been told you have Peyronie's disease or cavernosal fibrosis, or you have a penile implant. All of these are contraindications to injection.[6 8]
- Your heart has limited what you can do, or you have had a heart attack, stroke, unstable angina or a dangerous rhythm, or your heart has not been assessed recently.[6 21]
- You take warfarin, heparin or any other blood thinner, or you have a condition that interferes with clotting.[6 8]
- You have been told you have a venous leak in the penis, since alprostadil can reach the rest of the circulation more readily and lower blood pressure.[6]
- Your eyesight, your hands or your memory would make it hard to draw up and inject an exact dose, or you would rather a partner learned to do it.[3]
- Please bring the full list of everything you take, prescription, over the counter and supplement.[3]

The alprostadil safety figures come from studies of up to 18 and 24 months, the longest well counted exposure published for any injected treatment.[6 8] The mixes have no comparable dataset: the clinic series followed men for one to five years without a control group, and what happens to the erectile tissue after fifteen or twenty years of injections has not been

measured for any of these preparations.

§ 08

Is this right for you

Injection therapy suits a man who wants it, whose heart can take sexual activity safely, who has no condition that makes it unsafe, and who is willing to learn the technique. The AUA sets out the assessment plainly: a thorough medical, sexual and psychosocial history, an examination including pulse, resting blood pressure, waist measurement and the genitals, and selective blood tests, with a short validated questionnaire to measure change against.[3]

Before we begin

- [ ] Your medical history, how the problem started and changed, your current medications and supplements, and your partner's view where that helps[3]
- [ ] Pulse, resting blood pressure, waist measurement and an examination of the penis, so that any existing bend, lump or firm band is recorded before the first injection[3 21]
- [ ] Baseline bloodwork of the kind the guideline describes: a morning total testosterone, and glucose or HbA1c and fasting lipids[3]
- [ ] A written note of your goals, so we can judge progress together

Finding the cause comes first, and treating it helps the man as well as the erection. Diabetes, high blood pressure, high cholesterol, smoking, sleep apnea, depression and several common medicines all contribute, and the AUA asks that every man be told that erectile dysfunction is a marker for conditions that need attention of their own.[3] Tablets are the usual first treatment, so if you have not had a full dose of one used correctly on several occasions, that is worth doing before moving to a needle; our oral medicines guide (OCW WP 062) covers that ground. Injection is the second line step where tablets do not work, which includes most men after radical prostatectomy.[16]

Reviewing your progress

The first reviews are about the drug, the dose and the technique, and they happen in the office until the dose is settled.[3] After that the labels ask for a visit and an examination of the penis about every three months while injections continue, and for treatment to stop if a bend or a firm band appears.[6 8] If one preparation is not enough, another may be, and the sequential programme showed that most men who failed one agent responded to the next.[15] Some men find their natural or tablet assisted erections return and stop injecting altogether.[13] Your physician will set your own schedule, and you are welcome to stop at any time.

> **QUESTIONS TO ASK YOUR PHYSICIAN**
>
> What is causing my erectile dysfunction, and has it been looked for? Is my heart fit for sexual activity? Should I try a tablet properly first, and have I? Which preparation are you recommending for me, and is it FDA approved or compounded? What exactly do I do if an erection will not go down, and who do I call at two in the morning? How often will my penis be examined, and what are you looking for? What would make you change or stop this treatment?

We are glad to answer all of these.

§ 09

Regulatory status

Alprostadil. Alprostadil for injection into the penis is FDA approved, as Caverject and Caverject Impulse and as edex, for the treatment of erectile dysfunction and as an aid to diagnosing it.[6 8] It is a small molecule drug rather than a biologic, and it is not a controlled substance. Using it at a dose or in a way the label does not describe would be off label, which a physician may lawfully do.

The three mixes. Bi Mix, Tri Mix and Quad Mix are not FDA approved. No combination injection for erectile dysfunction has ever been approved in the United States, so there is no standardised mixture and no agency reviewed dose; each preparation is compounded by a pharmacy to the physician's instructions.[3] Compounded medicines are not FDA approved, and the FDA does not review their safety, effectiveness or quality before they are sold.[10] They are prepared either by a state licensed pharmacy under section 503A, against a prescription for one named patient, or by an outsourcing facility registered with the FDA under section 503B.[22] Using a combination injection for erectile dysfunction is an off label use, and both alprostadil labels state that combinations with other vasoactive agents have not been established in clinical studies and are not recommended.[6 8]

The individual ingredients. Phentolamine and atropine injections are FDA approved, but for other conditions, so their use in the penis is off label.[4] Papaverine injection has no FDA approval of any kind: it is marketed as an unapproved drug, and its label states that it is not indicated for treating impotence by injection into the penis and that such injection has caused persistent priapism requiring medical and surgical intervention.[4 9] The AUA puts the position plainly, that the injectable agents other than prostaglandin have been used successfully for decades and that none is formally FDA approved for this indication.[3] Your physician will tell you which drugs are in the preparation written for you.

Athletes. The World Anti Doping Agency Prohibited List in force from 1 January 2026 does not name alprostadil, prostaglandin E1, papaverine, phentolamine or atropine in any of its classes, so none of them is prohibited in or out of competition, and none appears in the Monitoring Program.[23] The list is revised every year, so a tested athlete should confirm it with his own anti doping organisation each season.[23]

If you would like details about the preparation used in your treatment, please ask.

§ 10

Common questions

Which of these is FDA approved?

Alprostadil alone is FDA approved for injection into the penis, as Caverject and edex, both for treating erectile dysfunction and for helping to diagnose it.[6 8] Bi Mix, Tri Mix and Quad Mix are compounded combinations and are not FDA approved, and no combination injection for this purpose has ever been approved here.[3 10] If you would like details about the preparation used in your treatment, please ask.

Does it hurt?

The needle itself is very fine and most men are surprised by how little they feel it. The ache that some men get comes from the drug rather than the puncture, and it is much commoner with alprostadil alone: 37 percent of men in the Caverject studies reported it at least once, usually mild or moderate, and with edex it accompanied 15 percent of injections and faded from 41 percent of men in the first two months to 3 percent by months 21 to 24.[6 8] Across the studies the AUA extracted, pain with injection averaged 2.0 percent for Tri Mix and was not reported in the Quad Mix arms.[3]

Why a mix instead of alprostadil on its own?

Mixes are used when alprostadil alone gives too little effect or too much ache, and the clinic series support that: in a programme of 625 men, 72.6 percent of those who had not responded to a simpler preparation responded to the three drug mix, and pain rates with the mixes are lower in the literature.[15] [3] What you give up is regulatory standing and evidence: the mixes are not FDA approved, the alprostadil labels do not recommend combining it with other vasoactive drugs, and the one randomized comparison found Tri Mix gave the same rigidity and satisfaction as prostaglandin E1 alone with longer erections and more priapism. [19] [6]

What do I do if the erection will not go down?

Call us as soon as it passes two hours. Try to ejaculate, then take oral pseudoephedrine and hold an ice pack to the penis for 30 to 60 minutes, as the AUA suggests; if a painful, rigid erection is still there, be at an emergency room within 2 to 4 hours of the injection.[3] Past 4 hours it is priapism, a medical emergency that can scar the erectile tissue and leave permanent erectile dysfunction, and the first treatment there is an injection of phenylephrine, which worked in 71 to 93 percent of reported cases. [7] [6]

How likely is that, really?

With alprostadil the label figures are a prolonged erection of 4 to 6 hours in 4 percent of 1,861 men and priapism beyond 6 hours in 0.4 percent, and the edex studies found priapism in under 1 percent of 1,065 men over 24 months.[6] [8] With the mixes the published averages are higher, 5.5 percent for Bi Mix, 3.2 percent for Tri Mix and 4.8 percent for Quad Mix, although a large clinic programme using mostly Tri Mix recorded only 0.5 percent. [3] [13] Titrating the dose in the office and keeping to it is what moves you toward the low end of those ranges. [3]

Will this damage the penis over time?

Scar tissue inside the shaft is the long term concern, and it is why we examine you. The Caverject label reports fibrosis in 3 percent across its studies and 7.8 percent in one 18 month self injection study, and the edex label 7.8 percent including Peyronie's disease over 24 months.[6] [8] Across the wider literature no single drug or combination was clearly worse than the others, and the proportion reporting fibrosis did not rise with longer follow up, though nobody has followed a defined group beyond a few years. [3]

Can I inject it myself, and do I have to come in first?

Yes to the first, after the second. The alprostadil labels require the first injections to be given in the office with the dose titrated there and the man staying until the erection has settled, and they ask that your technique be assessed before you take it home; the AUA asks for the same test for every injected agent, compounded ones included.[6] [8] [3] A partner can be taught to give the injection instead, and that works well for some couples.

Where is a compounded medicine made, and who oversees it?

Federal law sets out two kinds of compounding. Under section 503A, a state licensed pharmacy or physician prepares a medicine for one patient against that patient's own prescription, and the state board of pharmacy carries the day to day oversight while the FDA inspects for cause and on surveillance.[10] Under section 503B, an outsourcing facility registers with the FDA, works to federal manufacturing quality standards, reports adverse events and the products it makes to the agency, and is inspected by the FDA on a risk based schedule; it may also supply a clinic directly rather than for one named patient. [22] We use both kinds, and which one prepares your medicine depends on the preparation.

Is a compounded medicine the same as an FDA approved one?

No, and the difference matters. A compounded preparation is not FDA approved, and the agency does not check its safety, effectiveness or quality before it is sold, which is why an approved product is the first choice whenever one fits your situation.[10] What a prescription from a licensed pharmacy or a registered outsourcing facility does give you is a named

prescriber, a facility answerable to a state board or to the FDA, ingredients that meet federal requirements, and a route for reporting a problem. A vial bought online and labelled for research use only has none of that: the FDA treats those products as unapproved new drugs when they are meant for people, and has written to the companies selling them. [24] Please do not use one.

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