Understanding klinefelter syndrome

LAWLEY Hormone Solutions

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What is Klinefelter Syndrome?

Klinefelter syndrome is the most common cause of male infertility. It is a sex chromosome variation that occurs in 1 in 500 males. Most men do not demonstrate symptoms. Normally, males have one X chromosome in their cells. Males affected with Klinefelter syndrome have at least one extra X chromosome in most of their cells. The extra chromosome impacts their:

- Bone strength
- Breast size
- Energy level
- Hair growth
- Height
- Hip girth
- Language development
- Learning
- Muscle mass
- Social development
- Thought processes

Not all men with KLINEFELTER SYNDROME are 100% infertile. ICSI can produce a child – see page 9.

Klinefelter syndrome is also known as XXY syndrome.

How can I detect it?

Babies and Toddlers

A geneticist can diagnose Klinefelter syndrome before your son is born through a fetal cytogenetic analysis.

Your pediatrician may suspect Klinefelter syndrome if your infant son has:

- Developmental delay
- Undescended testicles (cryptorchidism)
- Pea-sized testicles
- Hypospadias (urine dribbles out of an opening on the underside of his penis)

However, 75% of boys with Klinefelter syndrome develop normal height and weight until they reach age 4 or 5. In 25% of boys, there is a telltale condition called clinodactyly, where the little finger curves toward the ring finger because the middle bone is wedge-shaped instead of rectangular.

School-age Boys

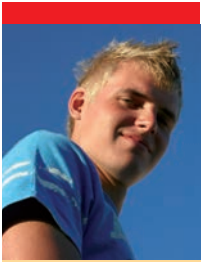
Your pediatrician may investigate your school-age son for Klinefelter syndrome if he has this characteristic appearance:

- Tall stature
- Knock-knees (genu valgum)
- High arches (pes cavus)
- Protruding lips
- Projecting jaw (prognathism)
- Very widely-spaced eyes (hypertelorism)
- If he is Caucasian or Black, epicanthal skin folds on his upper eyelids at the inner corner, giving him an oriental look
- Poor coordination
- Fused bones in his forearms that make it difficult for him to rotate his arms (radioulnar synostosis)
- Quiet, tractable personality with occasional tantrums and aggression

You may ask your pediatrician to investigate your son for Klinefelter syndrome if he has:

- Attention Deficit Disorder (ADD)
- Learning disability (especially dyslexia, reading difficulty, and data retrieval problems)
- Mental retardation (IQ drops 15 points for each additional X chromosome)
- Poor expressive and receptive language skills
- Poor short term memory
- Osteoporosis (bone thinning)
- Lack of sporting ability

Puberty



Your doctor may suspect Klinefelter syndrome when your boy reaches puberty if he has:

- High-pitched voice
- Sparse beard and body hair
- Gynecomastia (enlarged breasts)
- Feminine fat distribution
- Taurodontism (enlarged molar teeth)
- Breast cancer or germ cell tumors from elevated estradiol

If your doctor suspects your son has the androgen deficiency that accompanies Klinefelter syndrome, he will likely be sent to a lab for these blood tests:

- FSH (follicle stimulating hormone)
- LH (luteinizing hormone)
- Estradiol
- Testosterone

You may ask your doctor to perform genetic screening for Klinefelter syndrome if your son exhibits:

- Inability to deal with stress
- Psychological problems, like anxiety, neurosis, depression, or psychosis

When should I tell my son he has Klinefelter syndrome?

Experts recommend explaining to your affected child that he has Klinefelter syndrome when he reaches his mid-to-late teens. He should be old enough by then to understand its implications. Give him this booklet. Knowing that there is hope may help him to deal with his symptoms.

Adult Men

Most men with Klinefelter syndrome do not exhibit symptoms. You may first notice a problem when you experience:

- Lack of libido
- Sexual Dysfunction (SD)
- Infertility
- Varicose veins that tend to ulcerate or clot (thrombosis)
- Mitral valve prolapse
- Poor self-esteem
- Psychological distress

Klinefelter Facts

- Girls do not develop Klinefelter syndrome
- It does not occur more in one race than any other
- Klinefelter syndrome does not decrease the longevity of boys
- Most males with the syndrome are undiagnosed until adulthood, when they have reproductive problems
- Older mothers tend to produce more Klinefelter syndrome babies

What are the variants?

- 80% – 90% of affected boys have 47,XXY (one additional X chromosome). Most boys with the 47,XXY karyotype have normal intelligence.
- 10% have mosaicism (46,XY/47,XXY). Men with Klinefelter syndrome mosaicism are often fertile and can father a child through modern technology.
- Very rare and more serious variants are 48,XXYY; 48,XXXY; 49,XXXYY; 49,XXXXY; 47,X,i(Xq)Y and 47,X,del(X)Y). Boys with these rare variants have mental retardation that increases with more X chromosomes.

Statistics

- Most males who are infertile and have small testicles (grape size) due to a chromosomal disorder have Klinefelter syndrome with a 47,XXY karyotype (extra X and Y chromosomes) or a variant.
- In Australia, 1 in 650 males is born with Klinefelter syndrome. In the U.S.A., 1 in 500-1,000 males has an extra sex chromosome. Klinefelter syndrome is significantly under-diagnosed in the general population. If your healthcare practitioner is unfamiliar with the finer details of Klinefelter syndrome, there is a list of references at the end of this booklet.

What causes Klinefelter syndrome?

Klinefelter syndrome occurs after the mother's egg is fertilized. Chromosome pairs are supposed to separate, so that two daughter cells receive one chromosome each. In Klinefelter syndrome, the pair does not disjoin (separate). Both of the chromosomes in the pair go to one daughter cell. The other daughter cell receives none. This problem happens more frequently in older mothers, and is called meiotic nondisjunction.

As a result of this genetic problem, the Klinefelter syndrome baby develops an abnormal pituitary gland, testicles, and hypothalamus portion of the brain. The boy's testicles degenerate, so they cannot produce enough sperm in later life. Healthy tissue is replaced by clear, glassy collagen fibers, called hyaline. The boy has scar tissue (fibrosis) in his seminiferous tubules, where his sperm form. Feminine breasts develop in late puberty for 50% of Klinefelter syndrome adolescents. Urine tests show elevated gonadotropin levels, which mean the male is sterile. Psychosocial problems and low self-esteem result from the feminizing effects of the hormone estradiol.

Who discovered the syndrome?

Dr. Harry Klinefelter discovered the syndrome while working with nine male patients at Massachusetts General Hospital in Boston in 1942. The actual genetics were worked out later, from 1956 – 1959 by Drs. Joe Hin Tjio, Albert Lavan, and Patricia Jacobs.

What are my treatment options?

Boys with Klinefelter syndrome do not need a special diet, or to restrict their activities. Hospital care is not required. Treatment is on an out-patient basis.

Testosterone is the treatment of choice for Klinefelter syndrome. Testosterone can reduce the gonadotropin level to high normal. Gradually, testosterone will virilize the boy, giving him male secondary sex characteristics, like a beard, body hair, and a male-pattern fat distribution.

When your son is 11 or 12 years old, the doctor will commence testosterone supplementation. Testosterone treatment options include injections, gels and scrotal cream.

Common testosterone injections options include:

Drug name	Trade Name
Testosterone enanthate	Delatestryl® Primoteston® Depot
Testosterone esters	Sustanon®
Testosterone cyprionate	Depo-Testosterone
Testosterone undeconate (slow release)	Reandron®, Nebido® Not available in the USA

Testosterone injection treatment (using short-acting injections) usually begins with a 50mg dose on a monthly basis.

Transdermal gels (1% testosterone gel AndroGel®, Testogel® or Testim®) can be applied daily to the arms, chest, back and shoulders.

Testosterone cream (AndroForte® 2 and AndroForte® 5) can be applied either transdermally, but preferably scrotally once daily.

The doctor will closely monitor your son's growth and the development of male secondary sex characteristics. Your son will need to have blood drawn to check the gonadotropin hormone levels.

In years past, adult males with Klinefelter syndrome visited the doctor every two or three weeks to receive an intramuscular injection of 200 – 250 milligrams of testosterone enanthate, esters or cyprionate or at 6-monthly intervals for 600 –1000 milligrams testosterone implants.

More recently testosterone gels (AndroGel®, Testogel® and Testim®) have allowed patients to self administer their testosterone requirements. Testosterone gels are applied to the body - abdomen, chest, shoulders and arms.

AndroForte® 2 and AndroForte® 5 scrotal testosterone creams are the most recent and user friendly advance in testosterone administration. Scrotal skin is significantly more receptive to testosterone absorption due to its high blood flow, thin skin and low fat content. Testosterone cream applied to the scrotum achieves significantly higher testosterone blood levels than the equivalent amount of testosterone applied to other areas of the body. This represents signifi cant cost savings to patients. Because testosterone gels are alcohol based they cannot be applied scrotally due to the sensitivity of scrotal skin.

Unlike intramuscular injections and implants, the cream is painless. The daily dose you receive with cream is even. Injections produce uneven testosterone blood levels because they wear off and have to be replenished every 7 – 22 days.

Specialists

You and your child can also benefi t from consulting with these specialists:

Geneticist: A geneticist can diagnose Klinefelter syndrome before your son is born through a fetal cytogenetic analysis. A genetic counselor may help you explain Klinefelter syndrome thoroughly to your affected son.

Endocrinologist: A hormone specialist can regularly monitor the effectiveness of the testosterone replacement therapy. The endocrinologist will order blood tests for testosterone, FSH, LH, and estradiol. The endocrinologist may order an echocardiogram for mitral valve prolapse, x-rays, and a bone density test for osteoporosis.

Physiotherapist (PT): Your affected son may have weak, fl accid muscles and slow refl exes (hypotonia). Klinefelter syndrome could make him clumsy, unbalanced, uncoordinated, and with poor posture. Ask your family physician to refer you to a physiotherapist familiar with Klinefelter syndrome.

Speech therapist: Your son may require help to understand complex language before he starts school. Ask your family physician for a referral to a speech therapist.

Occupational Therapist (OT): Your son may have motor dyspraxia, a nervous system disorder where he has diffi culty planning and executing complex movements and tasks. Obsolete terms for dyspraxia are clumsy child syndrome, congenital maladroitness, and sensory integration disorder. Dyspraxia often co-occurs with learning disabilities, dyslexia, and attention defi cit disorder. An Occupational Therapist (OT) can train your son to appear less clumsy. The OT can fi t your child with small, inconspicuous, and inexpensive assistive devices, like pen grips.

Psychologist: Enlarged breasts place psychological stress on affected men, so seek help from a psychologist familiar with Klinefelter syndrome. Visit The Australian Psychological Society at www.psychology.org.au to fi nd a local psychologist suitable for your needs. The American Psychological Association at www.apa.org offers a similar service.

Special Ed: Get a thorough psychoeducational examination through your son's school. The written evaluation you will receive from the Special Education Department lists your son's strengths and weaknesses, and recommends an appropriate classroom placement. A psychoeducational exam will list additional resources available in your area, so you can tailor your son's education.

Surgeon: You may want to consult a surgeon about mastectomy (breast removal) or breast reduction. Around 10% of XXY males have breast enlargement great enough to require surgery. Gynecomastia increases the chance of breast cancer.

Fertility Experts: Not all men with Klinefelter syndrome are infertile. Some have oligospermia (low sperm production). If you wish to father a child and have a low sperm count, a fertility expert may be able to extract sperm directly from your testicles during a biopsy, choose one that is viable, and inject it into a woman's egg. This process is called ICSI (intracytoplasmic sperm injection). The resulting child will not have a risk of developing Klinefelter syndrome above that of the general population. If the specialist fi nds more than one viable sperm, you may choose to have them frozen for future pregnancies. To date, more than 60 children have been born to Klinefelter men around the world through ICSI.

Role of Testosterone in Humans

Natural testosterone is a steroid hormone, normally produced by the Leydig cells in the testes of humans and animals. Females produce far less testosterone in their ovaries than males do in their testicles. The small amount of testosterone present in females does not have a masculinizing effect on them. Testosterone increases libido and affects mood in both sexes.

Testosterone is classifi ed as an androgen (masculinizing substance). Androgens control masculine secondary sex characteristics, like male hair growth patterns (beard, armpits, chest and groin), deep voice, and male fat distribution. Testosterone is crucial for the development and maintenance of the male sex organs (testes and penis).

Testosterone is also an anabolic, meaning it encourages bulky, strong muscle growth. Testosterone has systemic anabolic effects. It infl uences fluid balance by making the male retain electrolytes (sodium, potassium, and chloride), water, and nitrogen. Testosterone infl uences bone growth by encouraging the retention of calcium and phosphate. Testosterone makes the skin more vascular and less fatty.

Riding the Lifecycle

Testosterone production increases when a boy enters puberty. Testosterone production decreases when a man turns 50. A good testosterone target range for an adult Klinefelter man to maintain is 300 – 1,000 nanograms per deciliter (ng/dl) of blood serum (or 10.5 – 35 nmol/L). Ideally the level should be greater than 500 ng/dl.

Applying 1 gram (50mg testosterone) of AndroForte® 5 natural testosterone cream every night to your scrotum will help maintain this target range. Allow the cream to absorb into the skin before dressing. Wash your hands well with soapy water after use.

Lowering Testosterone

You may inadvertently lower your testosterone level by consuming foods containing too much protein and too few carbohydrates. If you go on a fad diet with too many carbs and too little fat, it can deplete testosterone. Other factors, separate to Klinefelter Syndrome that may lower testosterone levels include:

- Acute critical illness, burns, major trauma or surgery
- Drug use (e.g., opiates, glucocorticoids, anabolic steroids, some anticonvulsants)
- Chronic disease and its treatment
- Alcohol abuse
- Smoking
- Ageing

Most of the above cause an increase in Sex Hormone Binding Globulin (SHBG). SHBG is a transporter protein found in the blood. It acts as a

carrier to move hormones around the body.

Up to 99% of testosterone produced is bound to SHBG. Once bound to SHBG the testosterone is inactive.

Testosterone to which SHBG does not attach is the biologically available testosterone that is free to act on cells throughout the body (free testosterone).

You can marginally increase your testosterone level with exercise. To produce enough testosterone, your body requires the:

- Minerals boron and zinc
- Vitamins A, B6, and C
- Branched Chain Amino-acids (BCAA) valine, isoleucine, and leucine

Other Benefits of Testosterone

Testosterone supplementation helps boys and men with Klinefelter syndrome immensely, but it also benefits people with other conditions:

- Testosterone is the primary hormone responsible for sexual function, sexual motivation, sexual arousal and fantasy in men of all ages
- Testosterone is responsible for maintaining muscle mass and muscle strength
- AIDS patients often use testosterone to curtail unwanted weight loss and muscle wasting
- Testosterone plays a pivotal role in bone metabolism Testosterone slows bone loss and builds replacement bone
- Cancer patients who have had their testicles removed or suffered permanent and irreversible testicular damage due to chemo or radiotherapy may use testosterone to compensate for the loss
- Testosterone exerts an strong influence on mood, energy levels and concentration

- Androgen Deficient Ageing Males (ADAM) or late-onset hypogonadal males apply natural testosterone cream to combat their:
  - Changes in mood (fatigue, depression, anger)
  - Decreased body hair (feminization)
  - Decreased bone mineral density and possible resulting osteoporosis
  - Decreased lean body mass and muscle strength
  - Decreased libido and erectile quality
  - Increased abdominal fat
  - Rudimentary breast development (man-boobs or gynecomastia)
  - Low sperm in the semen

Women take reduced-dose testosterone to treat poor libido. This is a common "off-label" practice among doctors in the USA, where no testosterone product is officially approved for use by women. The situation in Australia is distinctly different. Lawley Pharmaceuticals produces a 1% testosterone cream (AndroFeme®), tailored especially for women. AndroFeme® is a popular testosterone treatment option for use in women because it involves no surgery, no pain, is applied by the woman in the privacy of her own home, and the dose is accurately controlled.

Homeopathic Treatments

Homeopathy is a complementary therapy. Homeopaths claim that like cures like. Essentially, homeopaths believe that if a substance causes a disease, then you can cure it by taking a very minute, diluted amount of the same substance. If you or your son have Klinefelter syndrome, you should know that homeopathic treatments contain NO testosterone nor have they been demonstrated to cause any change in testosterone levels. Testosterone is the worldwide gold standard for treating Klinefelter syndrome and androgen deficiency.

Potential Risks of Testosterone Treatment (Short and Long Term)

Testosterone should not be used in men with breast cancer or known or suspected prostate cancer.

Patients with heart disease, liver disease or kidney disease are not recommended to use testosterone supplements.

Before initiating TRT your doctor should check for prostate abnormalities by means of a digital rectal examination (insertion of the finger through the anus and feeling the hardness of the prostate gland) and a blood test for Prostate Specific Antigen (PSA).

These tests will ensure complications of the prostate should not arise due to testosterone usage.

Side effects can occur if testosterone is used in excess quantities. These may include:

- Too frequent or persistent erections of the penis (priapism)
- Nausea and vomiting
- Swelling of the ankles
- Acne
- Headache
- Gynecomastia (breast development)
- Increased appetite

These effects are usually associated with excessive levels of serum testosterone due to incorrect dose. Due to their mode of administration, testosterone gels and creams generally keep testosterone blood levels within the normal therapeutic range for men and therefore side effects are unlikely to occur.

Prostate Disease

A. Benign prostatic hyperplasia (enlarged prostate): The use of testosterone will increase the size of the prostate mainly during the first six months of treatment. Men with testosterone deficiency often have reduced prostate size and most increases in prostate size result in a return to "normal" prostate volume.

A number of medical studies have failed to show any deterioration in obstructive symptoms attributable to benign prostatic hyperplasia during treatment and urinary retention has not been reported at rates higher than in control subjects.

B. Prostate cancer: The most important theoretical danger of testosterone treatment is to increase the risk of developing prostate cancer. Whilst lowering of testosterone levels is a standard treatment for metastatic prostate cancer, there is no available evidence to suggest that replacement of low testosterone levels into the normal range, leads to any increase in the occurrence of the disease. Numerous medical papers have shown that there was no significant increase in the occurrence of prostate cancer and a variable increase in the levels of prostate specific antigen (PSA). The PSA is often below normal in hypogonadal men and is generally restored to normal with testosterone supplementation. The authors of one paper concluded that "there is no compelling evidence that testosterone has a causative role in prostate cancer... (nor) increases the risk". During the monitoring of testosterone replacement therapy, regular digital rectal examination and measurement of PSA are recommended.

Adverse Changes in Serum Lipids

Synthetic testosterone derivatives are associated with adverse changes in serum lipids. However, the use of pure testosterone (e.g. testosterone implants, patches, creams and gels) is not associated with any changes to cholesterol or serum lipid concentrations.

There is no known interaction between testosterone and lipid lowering medications.

Coronary Heart Disease

A major theoretical concern regarding testosterone administration is the possibility that it could increase the risk of cardio-vascular disease. Such a concept is based on the higher incidence of cardio-vascular events in men than in women. However, this may be much more readily explicable by protective effects of estrogen in women. There is little data to support a causal relationship between high testosterone levels and heart disease and in fact, a significant body of evidence suggests that the opposite may be true and that men with low testosterone levels may be at higher cardio-vascular risk. There are reports that testosterone replacement can improve symptoms of chronic stable angina and there are direct observations showing vasodilation following intra-coronary injections of

testosterone. There are no reports of increasing incidence of cardio-vascular disease including myocardial infarction, stroke or angina in reports of testosterone replacement therapy.

Polycythemia (an abnormal increase in red blood cells)

A well know side effect of chronic testosterone administration, particularly using the intra muscular route (injections), where high serum testosterone levels are present for some days following each injection, is the occurrence of polycythemia, with a rise in haematocrit (the percent of whole blood that is composed of red blood cells). It is noteworthy that men with hypogonadism tend to have anaemia and reduced hematocrit concentrations and testosterone replacement leads to normalisation. There is a direct dose relationship between the testosterone dose and the incidence of polycythemia. This effect, while not life threatening or severe requires the need for regular monitoring (yearly) by a medical professional of this parameter during testosterone replacement therapy.

Long term risks with testosterone replacement therapy are minimal, particularly in regard to the major concerns addressed above. Side effects from excessive testosterone dosing are noted, but such adverse reactions are extremely unlikely with testosterone cream or gel topical administration.

Contraindications

If you are a woman, you cannot take testosterone during pregnancy to avoid giving birth to a son with Klinefelter syndrome. The genetic problem already occurred when the cells divided and is irreversible. Do not take testosterone while you are breastfeeding, as it will adversely affect your child through the milk. The benefits do not outweigh the risks.

If you are a man, you cannot take testosterone if you have any of these pre-existing conditions:

- Known hypersensitivity or allergy to testosterone
- Existing cancer of the breast or prostate gland
- Severe heart, kidney, or liver disease
- Excessive calcium in the blood (hypercalcemia)

Precautions

Before you embark on a course of testosterone replacement therapy, or decide to place your son on TRT, take these simple precautions:

1. Ask your doctor to rule out these similar conditions before diagnosing Klinefelter syndrome:
   - Kallmann syndrome
   - 46,XX karyotype
   - Infertility
2. Get a blood test for testosterone. The normal range is 300 – 1,200 ng/dl or 10 – 35 nmol/L. It will be highest in the morning.
3. Your doctor needs to undertake a physical examination of your prostate gland and conduct a blood test to measure the PSA (prostate specific antigen). This is to ensure that you do not have prostate cancer. Testosterone should not be used if there is prostate cancer or irregularities. If you have chronic liver or kidney disease testosterone should only be used with strict medical supervision.
4. Get genetic testing to see if the cause is myotonic dystrophy.

In adult males, during therapy, get a regular (yearly) PSA test for early detection of prostate cancer and rectal examination of the prostate. You need regular hemoglobin, hematocrit, liver function, and cholesterol tests and frequent monitoring by your doctor for the risks discussed above.

What can we expect when we visit the doctor?

Your doctor will ask about your health and sex history, or that of your child. Your doctor will enquire about genetic disease in your family. Your doctor will ask you to list previous illnesses, drugs (prescribed and street drugs for recreational use), and stressors. Your doctor will perform a digital rectal exam to check for prostate cancer.

Explain to your child that he needs blood tests, x-rays, and a cardiogram. The x-rays and cardiogram do not hurt. The blood test is a minor prick. Accompany him during testing to make him feel secure. Maintain a calm demeanor. Bring a treat as positive reinforcement for your child's good behavior. Praise your child for his cooperation.

Which testosterone route is best for me?

If one Googles "natural testosterone cream" or "testosterone gel" there are dozens of products claiming to be the "best" and "authentic" natural testosterone creams or gel. Just how does a man determine which product is most suited to his requirements? The following is an outline of basic manufacturing processes to help you decide. The three quality standards of natural testosterone cream are:

1. **Pharmaceutical Grade:** The manufacturer operates to international standards of Good Manufacturing Practice (GMP). GMP means all production processes are standardized and controlled from the time the raw material is procured through to the expiry date printing on the finished product. The Australian government, like the U.S. and European regulators, enforces rigid government controls on the manufacturing facility and its equipment, processes, and packaging. AndroForte® 2 and AndroForte® 5 natural testosterone creams are guaranteed stable, effective, and potent. The final product has detailed documentation and is backed by clinical trials that substantiate its therapeutic claims.

2. **Cosmetic Grade:** This is the quality sold over-the-counter in drug, department and grocery stores. Cosmetic grade products are 70% pure. Often, brand-names have exactly the same ingredients as generics, just with a different label. Cosmetic grade products are allowed a high bacterial content, so their shelf-life is very limited (usually 3 – 6 months). Cosmetic manufacturers are not required to register their products with the government because cosmetic products do not require clinical trials to prove their worth.

3. **Compounded Product:** Natural health products from pharmacists, herbalists, homeopaths, naturopaths, and practitioners of traditional Indian and Chinese medicines are compounded. This means the product is tailored to the patient's individual needs in the delivery system most desired. Pharmacists compound drugs that are not commercially available, or in a different strength than that readily available. A compounded product may be needed to make a drug palatable. A compounded product may be needed if the patient reacts to dyes, preservatives, and allergens found in commercial products. Compounded products do not undergo any form of production control, concentration, impurity, stability or efficacy testing. Safe shelf-life is usually extremely short, if at all known. Compounded items are time-consuming to make, so generally they are more expensive.

The only pharmaceutical grade natural testosterone creams for men available worldwide are AndroForte® 2 and AndroForte® 5 cream from Lawley Pharmaceuticals, Australia.

AndroForte® 2 and AndroForte® 5 testosterone creams are specifically targeted for use in men with declined or lowered serum testosterone levels due to genetic disorders, surgical or chemical interventions or ageing. Low testosterone in men is associated with declined libido, diminished sexual function, fatigue, lethargy, loss of motivation, decreased muscle mass and strength, depression, irritability and mood changes. Applied topically to the skin, AndroForte® 5 and AndroForte® 2 Testosterone Creams for men are the world's only clinically trialed and tested pharmaceutical grade testosterone creams using natural bio-identical testosterone. AndroForte® 5 and AndroForte® 2 Testosterone Creams are listed with the Australian government (AUST L 166238 / L 166239).

AndroForte® Prescribing Information and Consumer Medicine Information can be downloaded from http://www.androforte.com (or by clicking on the links above)


AndroForte® 5
Cream containing 5% w/v (50mg/mL) Testosterone B.P. (17-β- Hydroxyandrost-4-en-3-one)
PRODUCT INFORMATION
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www.hormonesolutions.com

About Lawley Pharmaceuticals

Lawley Pharmaceuticals is a privately owned pharmaceutical company which focuses on the transdermal administration of the naturally occurring hormones testosterone, progesterone and estradiol.

Founded in 1995 by pharmacist Michael Buckley, Lawley Pharmaceuticals has grown to become a world leader in research and development of transdermal hormone preparations.

As the principal of Lawley Pharmaceuticals Mr. Buckley has presided over the development, research, clinical trial program, regulatory process, development and marketing of the company.

The Lawley Pharmaceuticals portfolio of products includes:

- AndroFeme 1% cream – Testosterone for women
- AndroForte® 2 and AndroForte® 5 creams – Testosterone for men
- Pro-Feme® 3.2% and 10% creams – Progesterone for women
- Natragen® 0.2% cream – Estradiol for women

Our Mission Statement

Lawley Pharmaceuticals provides optimal delivery systems for the administration of naturally occurring hormones to counter endocrine deficiency states.

Our philosophy centres on the principle to replace "like with like", to use a bio-identical hormone in preference to a synthetic hormone analogue when a viable clinical option and to advance areas of clinical research that has had little or no investigation using naturally occurring hormones.

Our goal is to establish, through evidence based medical research, bio-identical hormones as cornerstone treatments for diseases such as breast disease, infertility, male hypogonadism, female androgen deficiency, post partum depression and endometriosis.

Lawley Pharmaceuticals has established strong links with centres of medical excellence around the world and continues to push the boundaries of medical research.

Completed Clinical Studies

1. Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women. *Wren BG et al. Climacteric 2000 3:155–160.*
2. Distribution and metabolism of topically applied progesterone in a rat model. *Waddell B and O'Leary PJ. J Ster Biochem & Mol Biol. 80 (2002) 449–455.*
3. Plasma and saliva concentrations of progesterone in pre- and post-menopausal women after topical application of progesterone cream. *O'Leary PJ et al. Presented at the Annual Congress of the Australian Menopause Society held in Perth, Australia in October 1997*
4. Long-term pharmacokinetics and clinical efficacy of AndroForte 5 cream for androgen replacement in hypogonadal men. *Handelsman DJ et al. ANZAC Research Institute, Department of Andrology, Concord Hospital, Sydney, 2004.*
5. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. Goldstat R et al. *Menopause 2003; 10 (5): 390-398.*
6. The pharmacokinetics pilot study of ANDROFEME®1% testosterone cream following two week, once daily application in testosterone deficient women. Eden JA et al. *Presented at the 4th Annual Congress of the Australasian Menopause Society held in Adelaide 5-7th November 2000.*
7. A double-blind, randomized, placebo-controlled trial of the effect of testosterone cream on the sexual motivation of menopausal hysterectomized women with hypoactive sexual desire disorder. *El-Hage et al Climacteric 2007; 10: 335–343.*
8. Pharmacokinetics Of AndroForte 5 Cream: A Dose Finding Study. *Kelleher S et al. ANZAC Research Institute, Department of Andrology, Concord Hospital, Sydney, 2002.*

Recommended Reading for Patients

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2. http://www.nichd.nih.gov/health/topics/klinefelter_syndrome.cfm
3. Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, DHHS. (1997).

   Understanding Klinefelter Syndrome: A Guide for XXY Males and Their Families (97-3202).

   Washington, DC: U.S. Government Printing Office.
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8. http://ghr.nlm.nih.gov/condition=klinefeltersyndrome
9. http://www.genetic.org/knowledge/support/action/C130/
10. http://kidshealth.org/teen/sexual_health/changing_body/delayed_puberty.html
11. http://www.hormonesolutions.com.au/?page=pages/frontpage
12. http://www.lawleypharm.com.au/

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Glossary

You may hear these terms discussed in reference to yourself or your son:

Azoospermia: The ejaculate contains no sperm at all.

Cryptorchidism: Undescended testicles. One or both testes stay in the abdominal cavity as they are before birth, instead of entering the scrotum. The doctor can try to manipulate the testes down into the scrotum, or can move them surgically if manipulation fails. It is dangerous to leave the testes in the abdomen, as it increases the risk of testicular cancer. The testes need to be kept cool in the scrotum to produce sperm. The intense core heat of the abdomen kills sperm.

Fibrosis: Scar tissue replaces healthy tissue as a result of degeneration, injury, or infection.

Genotype: Genetic makeup, as opposed to appearance.

Gynecomastia: Enlargement of one or both male breasts, sometimes with milk production. This is not pubertal hypertrophy, where a tender disc of enlarged tissue forms under the boy's nipple and disappears within a year. Causes of gynecomastia include: Klinefelter syndrome; hormone imbalance; weight gain; taking steroids or estrogen; cirrhosis of the liver; tumor in the testicles, breast, or lung. Gynecomastia should always be evaluated by a doctor.

Hyalinized: Healthy tissue is replaced by hyaline (clear or translucent white, glassy collagen fibers) due to degeneration.

Hypospadias: A birth defect where the boy's urethra opens onto the underside of the penis or below it, instead of the end of the glans.

Hypothalamus: The section of the brain that regulates body temperature, chemical balance, the pituitary gland, and the autonomic nervous system. The hypothalamus is part of the limbic system, so it regulates sexual appetite, eating, sleep, and emotions. It influences heart and breathing rates and blood pressure. The hypothalamus is located in the grey matter, below the thalamus, in the center of the brain. The pituitary gland hangs on a stalk below the hypothalamus.

Karyotype: Number, form, and size of chromosomes.

Oligospermia: The ejaculate contains fewer sperm than normal.

Phenotype: The physical characteristics of the boy comprised of his genetic makeup and his environment.

Pituitary gland: Connected to the hypothalamus, the pituitary controls growth hormone, prolactin for milk production, and follicle stimulating hormone (FSH) to stimulate ovaries. The pituitary stimulates the adrenal glands and the thyroid.

Seminiferous tubules: Two or three convoluted tubes in the testicles, where sperm are made.

Gonadotropin levels: The pituitary gland secretes a group of hormones called gonadotropins, which stimulate the testicles and ovaries. Boys with Klinefelter syndrome possess at least one extra X chromosome(s), which usually causes their pituitary glands to produce too much of the gonadotropins FSH (follicular stimulating hormone) and LH (luteinizing hormone). FSH and LH suppress the testicles' normal function. Drs. S.K. Advani, M.D. Chadha, and N.M. Khan, endocrinologists in Bombay, reported examining two men in their twenties with 47XXY Klinefelter syndrome who did not have elevated FSH and LH. These doctors suggest all males with suspected Klinefelter syndrome should have a karyotype performed before starting therapy with hCG. If the karyotype test result shows 47 XXY and the serum gonadotropin levels are not elevated, then the males should undergo detailed imaging studies of their pituitary-hypothalamic complexes.

Internet Education Reference Sites

ANDROFORTE www.androforte.com
ANDROFEME www.androfeme.com
PROFEME www.profeme.com
NATRAGEN www.natragen.com
HORMONE SOLUTIONS www.hormonesolutions.com.au
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