For the use of an Endocrinologist or a Hospital or a Laboratory only.

Testosterone Gel 1% w/w

Cernos Gel

PANPI0533

Composition:

Each gram contains:	
Testosterone USP	10 mg
Gel Base	q.s.
Also contains Ethanol IP	67% w/w

Description:

Cernos Gel is a clear, colourless hydroalcoholic gel containing 1% testosterone. **Cernos Gel** provides continuous transdermal delivery of testosterone, the primary circulating endogenous androgen, for 24 hours following a single application to intact, clean, dry skin of the shoulders, upper arms and/or abdomen.

Mechanism of Action

Physiologic amounts of testosterone is released from this formulation; producing circulatory testosterone concentrations that approximate normal levels seen in healthy men.

Endogenous androgens including testosterone and dihydrotestosterone (DHT) are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include impotence and decreased sexual desire, fatigue, loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis. Drugs in the androgen class also promote retention of nitrogen, sodium, potassium, phosphorous and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism.

Pharmacokinetics

Cernos Gel is a hydroalcoholic formulation that dries quickly when applied to the skin surface. The skin serves as a reservoir for the sustained release of testosterone into the systemic circulation. Approximately 10% of the testosterone dose applied from this formulation is absorbed into the systemic circulation. Absorption of testosterone into the blood continues for the entire 24 hour dosing interval. Serum concentrations approximate steady state by the second or third day of the dosing.

With single daily applications of the gel, follow up measurements 30, 90 and 180 days after starting treatment have confirmed that serum testosterone concentrations are generally maintained within the eugonadal range. Circulating testosterone is chiefly bound in the serum to sex hormone binding globulin (SHBG) and albumin. The albumin bound fraction easily dissociates from albumin and is presumed to be bioactive. The portion of testosterone bound to SHBG is not considered biologically active. The amount of SHBG in the serum and the total testosterone level will determine the distribution of bioactive and nonbioactive androgen. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound and the rest is bound to albumin and other proteins.

There is considerable variation in the half life of testosterone, ranging from 10 to 100 minutes. Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and DHT. DHT binds with greater affinity to SHBG than testosterone. DHT concentrations increased in parallel to testosterone concentrations during treatment with this formulation.

About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic and sulphuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver. In patients treated with this formulation, there are no observed differences in the average daily serum testosterone concentration at steady state based on age, cause of hypogonadism or body mass index. No formal studies were conducted involving patients with renal or hepatic dysfunction.

Indications:

Cernos Gel is indicated **for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone**:

1) **Primary hypogonadism** (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone levels and gonadotropins (FSH, LH) above the normal range.

2) **Hypogonadotropic hypogonadism** (congenital or acquired) - Idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma or radiation. These men have low testosterone serum levels but have gonadotropins in the normal or low range.

Contra-indication:

- Known hypersensitivity to any component of the formulation or testosterone chemically synthesized from soy.
- In men with known or suspected prostatic carcinoma or carcinoma of the breast.
- **Cernos Gel** is not indicated for use in women.

Warnings and Precautions:

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis and jaundice). Peliosis hepatis can be a life threatening or fatal complication. Long-term therapy with testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas. Testosterone is not known to produce these adverse effects.

Testosterone gel should be used only if hypogonadism has been demonstrated and if other etiology, responsible for the symptoms, has been excluded before the treatment is started. There is no consensus about age specific testosterone reference values, however, it should be taken into account that physiologically testosterone serum levels are lower with increasing age. To ensure proper dosing, serum testosterone concentrations should be measured.

Elderly patients treated with androgens may be at more risk for the development of prostatic hyperplasia and prostatic carcinoma. Elderly patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of therapy. In men receiving testosterone replacement therapy, surveillance for prostate cancer should be consistent with current practice for eugonadal men.

Edema, with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be considered.

Gynecomastia frequently develops and occassionally persists in patients being treated with hypogonadism. Testosterone esters may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung disease.

If no precaution is taken, testosterone gel can be transferred to other persons by close skin to skin contact, resulting in increased testosterone serum levels and possibly adverse effects (e.g., growth of facial and/or body hair, deepening of the voice, irregularities of the menstrual cycle) in case of repeat contact (inadvertent androgenization). To minimize the potential of transfer of testosterone from gel treated skin to another person the following precautions should be taken: Patients should wash their hands immediately with soap and water after application of the gel; the application site should be covered with clothing after the gel has dried up; shower before any situation in which a skin contact is foreseen. In the event that unwashed or unclothed skin to which testosterone gel has been applied does come in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.

According to *in vitro* absorption studies on testosterone conducted with testosterone gel, it seems preferable for patients to observe atleast 6 hours between gel application and bathing or showering. To guarantee partner safety, the patient should be advised to observe a long interval between gel application and sexual intercourse or to shower before sexual intercourse. Changes in body hair distribution, significant increase in acne or other signs of virilization of the female partner should be brought to the attention of the treating physician.

Testosterone gel should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria), due to bone metastases. Regular monitoring of serum calcium concentrations is recommended in these patients. Caution is also advised in patients with ischemic heart disease and hypertension.

Hemoglobin and hematocrit levels should be checked periodically (to detect polycythemia) in patients on long term androgen therapy. Liver function, prostatic specific antigen, cholesterol and high density lipoprotein should also be checked periodically.

Testosterone gel is not a treatment for male sterility or impotence. If the patient develops a severe application site reaction, treatment should be reviewed and discontinued if necessary. Improved insulin sensitivity may occur in patients treated with androgens who achieve normal testosterone plasma concentrations following replacement therapy.

Testosterone gel should be used with caution in patients with epilepsy and migraine as these conditions may be aggravated. Certain clinical signs such as irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring dosage adjustment.

Since alcohol gels are flammable, fire or smoking should be avoided by the patient until the gel has dried.

Pregnancy & Lactation:

Testosterone gel is not indicated for women and must not be used in women.

Pregnant women should avoid any contact with testosterone gel application sites in men. This formulation may have adverse virilizing effects on the fetus. In the event of contact, wash with soap and water immediately.

Drug Interactions:

Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and therefore insulin requirements.

Concurrent administration of testosterone with ACTH or corticosteroids may enhance edema formation; thus, these drugs should be administered cautiously, particularly in patients with cardiac, renal, or hepatic disease. In one pharmacokinetic study of an injectable testosterone product, administration of testosterone cypionate led to an increased clearance of propranolol in the majority of men tested.

Increased monitoring of the prothrombin time and INR determinations are recommended. Patients receiving oral anticoagulants require close monitoring especially when androgens are started or stopped.

Androgens may decrease levels of thyroxin binding globulin, resulting in decreased T_4 serum concentrations and in increased resin uptake of T_3 and T_4. Free thyroid hormone levels, however, remain unchanged and there is no evidence of thyroid insufficiency.

Side effects:

Adverse effects possibly or definitively related to the use of testosterone gel include acne, alopecia, application site reaction, erythema, dry skin, asthenia, depression, emotional lability, gynecomastia, headache, hypertension, decreased libido, nervousness, breast pain, prostate disorder, testis disorder and abnormal laboratory test (which may include one or more of the following events: elevated hemoglobin or hematocrit, hyperlipidemia, elevated triglycerides, hypokalemia, decreased HDL, elevated glucose, elevated creatinine or elevated total bilirubin).

Other reported adverse effects are amnesia, anxiety, discolored hair, dizziness, dry skin, hirsutism, hostility, impaired urination, paresthesia, penis disorder, peripheral edema, sweating and vasodilation.

Overdosage:

Only one case of acute overdose following an injection has been reported in the literature. This was a case of a cerebrovascular accident in a patient with a high plasma testosterone concentration of 114 ng/ml (395 nmol/l). It would be most unlikely that such plasma testosterone concentrations be achieved using the transdermal route.

Dosage and Administration:

The recommended starting dose of **Cernos Gel** is 5 gm delivering 50 mg of testosterone systemically, applied once daily at the same time each day (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen.

Cernos Gel should not be applied to the genitals.

Serum testosterone levels should be measured approximately 14 days after initiation of therapy to ensure proper dosing. If the serum testosterone concentrations is below the normal range, or if desired clinical response is not achieved, the daily testosterone gel dose may be increased from 5 gm to 7.5 gm and from 7.5 gm to 10 gm.

Upon opening the packet(s), the entire contents should be squeezed into the palm of the hand and immediately applied to the application sites. Alternatively, patients may squeeze a portion of the gel from the packet into the palm of the hand and apply to application sites. Repeat until entire contents have been applied. Application sites should be allowed to dry for a few minutes prior to dressing. Hands should be washed with soap and water after testosterone gel has been applied.

Children: Testosterone gel is not indicated for use in children and has not been evaluated clinically in males under 18 years of age.

Disposal:
Used **Cernos Gel** packets should be discarded in a manner that prevents accidental application or ingestion by children.

Storage:
Store at temperature not exceeding 25°C. Do not freeze. Keep out of the reach of children.

Presentation:
Cernos Gel is available in 2.5 gm and 5 gm unit dose packets.

For further details, please write to:

SUN
PHARMA
Acme Plaza, Andheri-Kurla Road,
Andheri (E), Mumbai 400 059, INDIA.

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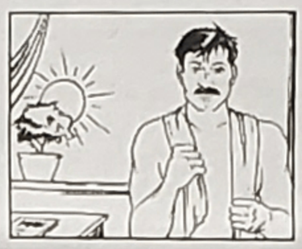
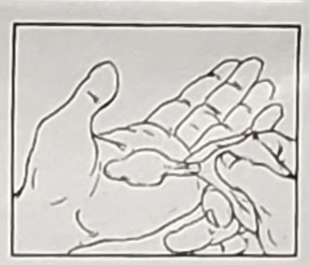
Cernos Gel Patient Information Leaflet

What is Cernos Gel ?
Cernos Gel is a formulation that delivers testosterone on topical application to skin and increases the testosterone levels to normal. The testosterone delivered by Cernos Gel is same as the testosterone produced in your body.
Testosterone supplement is indicated when there is deficiency of testosterone i.e.,Hypogonadism. Testosterone helps the body to produce sperms and for development of secondary sexual characteristics. Also, it helps to maintain bone strength and muscle mass and is necessary for normal sexual function & sex drive.

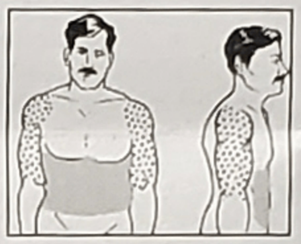
How should one apply Cernos Gel ?



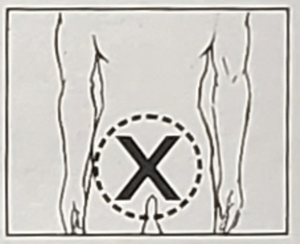
1. Apply Cernos gel (1 or 2 pouches as per instruction of your doctor) at the same time each day (preferably morning). If you take bath in the morning, apply Cernos Gel after your bath.
2. Ensure that your skin is clean and completely dry.
3. Squeeze the entire content onto the palm of your hand or squeeze one portion at a time, and continue until the pouch is empty.



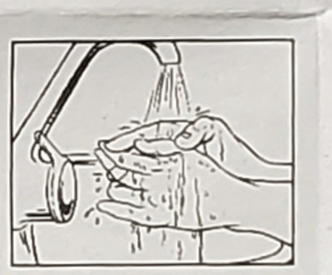
4. **Apply gel to the upper arm / shoulder areas or abdomen ONLY,** so as to ensure that your body absorbs the right amount of Testosterone.



5. **Please do not apply Cernos Gel to your genitals (Penis & Scrotum) or to skin that is not completely normal (open sores, wounds of irritations).**



6. Use circular motions to rub the gel for several seconds until the gel is well rubbed and the area feels dry.



7. Wash your hands thoroughly with soap and water immediately after application .
8. Allow Cernos Gel to dry for a few minutes before you dress, to prevent your clothing from wiping the gel off your skin.

9. Wait for at least 5-6 hours, incase you plan to take shower or swim after the application of gel, to ensure the greatest amount to get absorbed.
10. **Maintain normal activities,** once your hands are washed and the application site covered with clothing.

However, incase you expect direct skin contact with someone else, you must wash your application sites thoroughly with soap and water, so as to reduce the chance of medicine transfer to the other person.

Who should not use Cernos Gel ?
- Hypersensitivity to any of the component of the formulation.
- Must not be used by women and children.
- Pregnant and breast feeding women are especially at risk and should avoid skin contact with Cernos Gel applied sites in men. Testosterone may cause harm to fetus. While children, who normally, have low levels of testosterone, could be harmed by higher levels of the same.
- Not to be used in patients having prostate cancer or breast cancer (rare conditions in males).

What to do if other person comes in contact with Cernos Gel ?
Wash his or her area of contact thoroughly with soap and water as soon as possible. The longer the gel is in contact with the skin before washing, the greater is the chance that the other person will absorb some testosterone.

What are the possible side effects of Cernos Gel?
Please tell your doctor, if you develop any of the following side effects:
- Penis erections that are too frequent and continue too long.
- Nausea, vomiting, yellow or darker skin (jaundice) or ankle swelling.
- Breathing disturbances, including abnormal or stopping normal breathing while sleeping.
- Difficulty in urination.
- Any side effects that concern you.

Tell your doctor if your female partner develops changes in hair distribution, increases in acne or other signs of masculinity.
Older patients may be at the risk of developing enlarged prostate or prostate cancer. **This also may be monitored by periodic blood tests and prostate examinations.**

What to do if you miss a dose of Cernos Gel ?
If you miss a dose, do not double your next dose the next day to catch up. If your next dose is less than 12 hours away, it is best to wait. Do not take the skipped dose. If it is more than 12 hours until your next dose, take the dose that you missed.

Care to be taken while washing your clothes
- Your clothes should not be mixed with other household clothing while washing.
- Clothes should be washed separately, by keeping in detergent water for few minutes.
- Avoid direct contact with the parts of clothing exposed to Cernos Gel (Shoulder/ upper arm or abdomen).

Other Information :
- Do not give Cernos gel to other people, even if they have the same symptoms that you have.
- Keep Cernos gel in safe place.
- Tell your doctor about other medicines you are taking. Cernos Gel may alter the effects of these medicines.

* For patient information only

Keep Cernos Gel out of reach of Children

Cernos Gel
Testosterone Gel

Inca Life Sciences
a division of Sun Pharmaceutical Industries Ltd.