Supporting Document for Testogel® (testosterone) 50mg, gel in sachet

Details of Drug[1]

Name of the medicinal product	TESTOGEL 50 mg, gel in sachet
Qualitative and quantitative composition	One sachet of 5 g contains 50 mg of testosterone.
Brand name	Testogel
Manufacturer	Besins Healthcare (UK) Ltd Lion Court 25 Proctor Street London WC1V 6NY
Is the drug licensed in the UK?	Yes

Indications[1]

Licensed Indication	Testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests [1]

Mechanism of Action[1]

Mechanism of action	Testogel is a hydroalcoholic gel which when applied to the skin is rapidly absorbed into the stratum corneum layer which forms a reservoir that acts as a rate-controlling membrane. Testogel is then gradually diffused from this skin reservoir over several hours. Steady state plasma testosterone concentrations are reached approximately on the 2nd day of treatment with Testogel. [1,2]

1. Testogel Summary of Product Characteristics, Besins Healthcare, Aug 2018 https://www.medicines.org.uk/emc/product/6808/smpc Accessed July 2019
2. Wang C et al. J Clin Endocrinol Metab 2000;85:964-969

Dosage regimen and monitoring requirements of Testogel® (testosterone) 50mg[1]

Dosage Regimen	Cutaneous use. Adult and Elderly men The recommended dose is 5 g of gel (i.e. 50 mg of testosterone) applied once daily at about the same time, preferably in the morning. The daily dose should be adjusted by the doctor depending on the clinical or laboratory response in individual patients, not exceeding 10 g of gel per day. The adjustment of posology should be achieved by 2.5 g of gel steps. The application should be administered by the patient himself, onto clean, dry, healthy skin over both shoulders, or both arms or abdomen. After opening the sachets, the total contents must be extracted from the sachet and applied immediately onto the skin. The gel has just to be simply spread on the skin gently as a thin layer. It is not necessary to rub it on the skin. Allow drying for at least 3-5 minutes before dressing. Wash hands with soap and water after applications. Do not apply to the genital areas as the high alcohol content may cause local irritation.
Monitoring requirements	Prior to initiation of therapy, all patients must undergo a detailed examination in order to exclude a risk of pre-existing prostate cancer. During treatment, careful and regular monitoring of prostate gland and breast must be performed (digital rectal examination [DRE] and estimation of serum prostate specific antigen [PSA]) at least once yearly and twice yearly in elderly and at-risk patients (those with clinical or familial risk factors). Testosterone level should be monitored at baseline and at regular intervals during treatment. Clinicians should adjust the dosage individually to ensure maintenance of eugonadal testosterone levels. Beside laboratory tests of the testosterone concentrations in patients receiving long-term androgen therapy the following laboratory parameters should also be monitored regularly: haemoglobin, haematocrit (to detect polycythaemia), liver function tests, and lipid profile.

1. Testogel Summary of Product Characteristics, Besins Healthcare, Aug 2018
https://www.medicines.org.uk/emc/product/6808/smpc Accessed July 2019

Guidelines associated with testosterone therapy – Screening & Diagnosis [5-11]

In recent years, established specialist medical societies have produced guidance on the use of testosterone therapy (TTh) in men with testosterone deficiency (TD). These include:

- The British Society for Sexual Medicine (BSSM)[5]
- The European Association of Urology (EAU)[6]
- American Urological Association (AUA)[7]
- The Endocrine Society (ES)[8]

There is overall consensus among the guidance produced by these expert groups that a diagnosis of Testosterone Deficiency (TD) should only be made when patients have low total testosterone (TT) levels (using 2 Total Testosterone (TT) measurements taken on separate occasions, taken in early morning), combined with symptoms and/or signs [5-8]

The majority of guidelines also recommend routine screening for Testosterone Deficiency (TD) in men with the following conditions:

- Erectile Dysfunction (ED)
- Type 2 diabetes mellitus (T2DM)
- Obesity
- Chronic opiate use [5,7-10]

The British Society for Sexual Medicine guidelines on adult testosterone deficiency recommend basing decisions on therapy according to published action levels rather than laboratory reference ranges. The rationale for this is because reference ranges quoted by laboratories represent the normal population and that the action levels recommended by the BSSM refer to men with clinical symptoms of Testosterone Deficiency (TD).[5]

The action levels quoted by the BSSM are as follows:[5]

- Total Testosterone level <8 nmol/L or Free Testosterone level <0.180 nmol/L
    - **Usually requires Testosterone Therapy**
- Total Testosterone level >12 nmol/L or free testosterone level >0.225 nmol/L
    - **Does not require Testosterone Therapy**
- Total Testosterone level between 8-12 nmol/L or free testosterone level 0.180-0.225 nmol/L
    - **May require a trial of Testosterone Therapy for a minimum of 6 months**

BSSM guidelines also state:[5]

- A free testosterone (FT) level lower than 0.225 nmol/L provides supportive evidence for Testosterone therapy in the presence of appropriate symptoms.

In addition, the 2018 British Society for Sexual Medicine Guidelines on the Management of Erectile Dysfunction state that low testosterone is a frequent reason for failure to respond to Phosphodiesterase 5 inhibitors (PDE5i) and that correction of low testosterone levels <10.4nmol/L has been shown in multiple studies to restore the response to PDE5Is.[11]

Guidelines associated with testosterone therapy (TTh) – Benefits & Risks of Testosterone Therapy (TTh) in Testosterone Deficiency (TD) Patients [5]

British Society for Sexual Medicine (BSSM) Guidelines state:

- Beyond 6 months there is evidence of benefit for Testosterone Therapy (TTh) in body composition, bone mineralisation, and features of metabolic syndrome.
- Testsosterone Therapy (TTh) improves sexual desire, erectile function & sexual satisfaction.
- Decreases in bone mineral density (BMI) and waist size and improved glycaemic control and lipid profile are observed.
- Trials of Testosterone Therapy should be ≥6 months and maximal benefit is often seen beyond 12 months
- Fully inform the patient about expected benefits and side effects of therapy and facilitate a joint discussion by an informed patient and physician.
- Fully discuss the adverse effect of Testosterone Therapy (TTh) and its effect on future fertility for each patient and his partner and offer alternative treatment as necessary.
- In patients with adult-onset TD, when Testosterone Therapy (TTh) is prescribed, offer weight-loss and lifestyle advice as standard management.
- In severely symptomatic patients with Total Testosterone (TT) levels <8 nmol/L, lifestyle and dietary advice alone is unlikely to produce meaningful clinical improvement within a relevant clinical period.

Guidelines associated with testosterone therapy (TTh) – Follow up & monitoring [5,6,8]

British Society for Sexual Medicine (BSSM) Guidelines state:

- Aim for a target total testosterone (TT) level of 15-30 nmol/L to achieve optimal response.
- Prostate health should be assessed by digital rectal examination (DRE) and prostate specific antigen (PSA) before initiating therapy. Follow-up by PSA testing at 3, 6 and 12 months and DRE 3–12 months after initiating Testosterone Therapy (TTh), and thereafter annually for both.
- Check haematocrit at baseline, 3–6 months after starting treatment, and then annually. If haematocrit is >54% and remains high, consider stopping therapy and reintroducing at a lower dose or switching preparations.
- Assess cardiovascular (CV) risk before Testosterone Therapy (TTh) is initiated and monitor CV risk factors throughout therapy.
- Assess response to therapy at regular intervals within the first year and then annually thereafter.

Guidelines associated with the choice of testosterone therapy (TTh) in the initial treatment of patients with Testosterone Deficiency[12]

International Society for the Study of the Ageing Male (ISSAM) recommendations state:

- The selection of the testosterone therapy should be a joint decision of an informed patient and physician [12]
- Because the possible development of an adverse event (especially elevated haematocrit, or prostate cancer) during treatment requires rapid discontinuation of testosterone therapy, short-acting preparations may be preferred over the long-acting depot preparations in the initial treatment of patients with hypogonadism. [12]

5. Hackett G, et al. J Sex Med 2017;14:1504-23. 6. Dohle GR, et al. Guidelines of Male Hypogonadism. European Association of Urology 2015. Available at: uroweb.org/wp-content/uploads/18-Male-Hypogonadism_LR1.pdf Accessed May 2019. 7. Mulhall JP, et al. American Urological Association 2018. 8. Bhasin S, et al. J Clin Endocrinol Metab 2018;103(5):1715-44. 9. Garvey TW, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for Comprehensive Medical Care of Patients with Obesity. Available at: aace.com/files/guidelines/ObesityExecutiveSummary.pdf Accessed May 2019 10. American Diabetes Association. Diabetes Care 2019;42(Suppl.1):S34–S45. Available at: care.diabetesjournals.org/content/diacare/suppl/2018/12/17/42.Supplement_1.DC1/DC_42_S1_Combined_FINAL.pdf Accessed May 2019. 11.Hackett, G et al. J Sex Med. 2018 Apr;15(4):430-457. 12. Lunenfeld et al Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men Aging Male, 2015; 18(1): 5–15

Evidence for the Clinical Efficacy of Testogel® (testosterone) Therapy: [13-15]

What is the effect of Testogel on serum testosterone (and free testosterone) levels?[13-14]

Swerdloff et al conducted a randomised, multicentre, 6-month active-comparator study of 227 hypogonadal men taking daily testosterone gel (AndroGel*) at either 50mg or 100mg a day, or a testosterone patch (5mg daily) investigated the pharmacokinetics of testosterone gel after repeated daily dosing for 180 days. The study was double blinded until day 90 with respect to the testosterone gel groups and open label for the testosterone patch group.

- At Day 0 (baseline), average serum testosterone concentrations over 24 hours were below the normal adult range for all three groups (range 8.22-8.60nmol/L)
- On Days 30 and 90, after gel application, the average serum testosterone level (Cav) in the testosterone gel 100mg/day group was 27.46nmol/L, 1.4-fold higher than the testosterone gel 50mg/day group (Cav = 19.62nmol/L and 19.17nmol/L for Days 30 and 90, respectively), and 1.9-fold higher than the testosterone patch group (14.62nmol/L and 14.46nmol/L for Days 30 and 90, respectively) (p=0.0001).
- On Day 180, the serum testosterone concentrations that were achieved and the pharmacokinetic parameters were similar to those on Days 30 and 90, for patients who continued in their original randomised treatment groups.

Wang 2004 was an extension of the above study involving 123 hypogonadal men receiving testosterone gel (AndroGel*) for up to a further 36 months, confirmed the long-term maintenance of serum testosterone levels within the physiological range.

*** AndroGel is the trade name of Testogel outside of the UK**
**** The normal range in these studies differs from the British Society for Sexual Medicine (BSSM) guidelines[5]**

2. What is the effect of Testogel on the sexual & mood symptoms of hypogonadism?[14]

The primary aim of testosterone therapy is to return testosterone levels of hypogonadal men back into the normal range to alleviate the symptoms of testosterone deficiency. A number of clinical studies have investigated the effects of AndroGel* treatment on the clinical symptoms of hypogonadism.

Wang et al performed a 36 month extension study on 123 hypogonadal men who previously participated in a 6-month study comparing AndroGel* with a testosterone patch.

- After treatment with AndroGel*, sexual desire, sexual enjoyment and sexual activity improved, compared with baseline, and were maintained at the same level from 6 months until the end of the treatment period (p=0.0001).[14]
- Positive mood scores improved with treatment and were sustained (p=0.0022), whereas negative mood parameters were decreased and remained significantly lower (p=0.0013) than baseline without further changes after 6 months of AndroGel* therapy.[14]

*** AndroGel is the trade name of Testogel outside of the UK**

3. What is the effect of Testogel on body composition parameters in hypogonadal men? [14]

Wang et al demonstrated the following results on body composition parameters following treatment with AndroGel*:

- Average total body mass and lean body mass increased significantly vs baseline (p=0.0157 and p=0.0001, respectively), whereas fat mass decreased significantly (p=0.0058). The decreases in fat mass (p=0.032) and percent fat (p=0.0001) were observed only in the younger subjects but not in older men (>60years)
- Bone mineral density (BMD) of the hip and spine showed a significant (p=0.0004 and p=0.0001, respectively) and progressive increase with treatment.
- Bone markers indicated that there was an early phase in which there was decreased bone resorption and increased bone formation, and a later phase suggestive of continued bone formation but without a further decrease in bone resorption.
- Muscle strength tested via chest and leg press increased but did not reach statistical significance over time.

*** AndroGel is the trade name of Testogel outside of the UK**

4. What impact does Testogel treatment have on body composition and HRQoL in hypogonadal men?[15]

Behre et al performed a randomised, double-blind, placebo-controlled trial of testosterone gel on body composition and health-related quality-of-life (HRQoL) in men with hypogonadal to low-normal levels of serum testosterone and symptoms of testosterone deficiency over 6 months with 12 months open-label follow-up.

The primary endpoint of this study was to assess changes in lean body mass (LBM) after 6 months treatment with testosterone gel vs placebo. The change in LBM after 6 months was statistically significant in favour of testosterone. The mean increase in LBM was +1.28± 0.15 and +0.02 ± 0.10 kg in testosterone and placebo groups, respectively ($p < 0.001$ for group difference).

Over the next 12 months of the study there was no further increase in LBM in the group treated with testosterone but in the group previously on placebo and later treated with testosterone LBM increased significantly, and reached similar values at the end of the study as encountered in the group receiving testosterone during the double-blind phase of the study.

A secondary objective of this study was to assess changes in health-related quality of life (HRQoL). This was assessed using the ageing males symptoms (AMS) score. Testogel was associated with a significant reduction in mean AMS score at 6 months compared to placebo (-10.5 vs -7.2; $p<0.002$).[15]

13. Swerdloff R et al. J Clin Endocrinol Metab 2000;**85**:4500-4510
14. Wang C et al. J Clin Endocrinol Metab 2004;**89**:2085-2098
15. Behre HM et al. J Aging Male 2012;**15(4)**: 198-207

Safety Profile of Testogel® (testosterone) Therapy [13-14]

1. Clinical trials have demonstrated that Testogel is a well-tolerated treatment for male patients with hypogonadism[14]
2. Clinical trials have demonstrated good compliance with Testogel[13]

Evidence for the Safety Profile of Testogel® (testosterone) Therapy: [13-14]

1. Clinical trials have demonstrated that Testogel is a well-tolerated treatment for male patients with hypogonadism[14]

Testogel is contraindicated:
- in cases of known or suspected prostatic cancer or breast carcinoma[1]
- in cases of known hypersensitivity to testosterone or any other constituent of the gel[1]

Prior to testosterone initiation, all patients must undergo a detailed examination in order to exclude a risk of pre-existing prostatic cancer. Careful and regular monitoring of the prostate gland must be performed in accordance with recommended methods (digital rectal examination [DRE] & estimation of serum prostate specific antigen [PSA]) in patients receiving testosterone therapy at least once yearly and twice yearly in elderly patients and at-risk patients (those with clinical & familial risk factors). Androgens may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia.[1]

The most frequently observed adverse reactions with Testogel are skin reactions (10%): reaction at the application site, erythema, acne and dry skin. Other common side effects (>1/100, <1/10) include diarrhoea, dizziness, headache, gynaecomastia, prostatic disorder, changes in laboratory tests (polycythaemia, lipids), mastodynia, paraesthesia, amnesia, hyperaesthesia, mood disorders, hypertension, alopecia, urticaria, haematocrit increase, red blood cell count increase and haemoglobin increase.

As with other testosterone treatments, haematocrit and haemoglobin should be monitored periodically.[1]

Patients should wash their hands after application and avoid skin-to-skin contact with others to avoid potential testosterone transfer.[1]

Wang 2004 was a randomised, multicentre, study evaluating the long-term efficacy and safety of AndroGel* in 163 men aged between 19-68 years, the following safety results were observed:[14]

***AndroGel is the trade name for Testogel outside of the UK**

Skin Irritation

- Application site skin reaction occurred in 12/163 (7.4%) subjects (one was classified as moderate).
- One subject discontinued after 12 months of testosterone gel (5g) because of worsening erythema and rash.

International Prostate Symptom Score (IPSS) & Prostate Specific Antigen (PSA)

- Mean IPSS score did not change significantly across time with testosterone gel. None of the individual scores showed any clinically meaningful changes
- Baseline PSA level was 0.85ng/ml. With testosterone replacement there were significant increases in PSA levels over time ($p<0.001$).
    - Mean serum PSA was 1.11ng/ml at month 6 and showed no further significant increases with continued testosterone treatment ($P = 0.150$).
- 3 subjects (1.8%) aged >63 years whose serum PSA rose above the predetermined critical value of 5.5 ng/dl had T treatment stopped and had confirmed prostate cancer on biopsy.

Haematocrit

- Haemoglobin and haematocrit levels increased as anticipated, reaching a maximum level at 6-12 months with no significant increases thereafter.
- The number of subjects with high haemoglobin or haematocrit that required discontinuation was similar to other reports.
- Haematological parameters (haemoglobin, haematocrit) remain within the normal range during long term treatment with Testogel.[14]

The authors concluded that the safety parameters observed in the study were comparable with other delivery systems, and that as with all androgen replacement therapies, continuous vigilance is required for the monitoring of haemoglobin, haematocrit and serum prostate specific antigen (PSA) for values that are above the critical range.[14]

2. Clinical trials have demonstrated good compliance with Testogel [13]

Testogel is a transparent, colourless gel available in a single-dose sachet. It is applied to the shoulder, upper arm or abdomen.[1]

In a randomised, multicentre, 6-month study of 227 hypogonadal men (aged 19-68 years) with morning serum testosterone levels at ≤10.4 nmol/L, the mean compliance rate for the 50mg gel (N=73) and 100mg gel (N=78) were 93.3% and 96.5% respectively.[13]

1. Testogel Summary of Product Characteristics, Besins Healthcare, Aug 2018 https://www.medicines.org.uk/emc/product/6808/smpc Accessed July 2019
13. Swerdloff R et al. J Clin Endocrinol Metab 2000;**85**:4500-4510
14. Wang C et al. J Clin Endocrinol Metab 2004;**89**:2085-2098

Table 1. Testosterone products indicated for the treatment of male hypogonadism in the UK [3,4]

Testosterone Therapy	Manufacturer
Gels	
Testogel® 50mg/5g gel sachets	Besins Healthcare (UK) Ltd
Testogel® 16.2mg/g gel pump	Besins Healthcare (UK) Ltd
Tostran® 20mg/g gel pump	Kyowa Kirin Ltd Ltd
Testavan® 20mg/g gel pump	Ferring Pharmaceuticals
Injections	
Nebido® 1000mg/4ml	Bayer HealthCare
Sustanon® 250mg/1ml	Aspen Pharma Trading Ltd
Testosterone enantate 250mg/1ml	Alliance Pharmaceuticals
Oral	
Restandol Testocaps® 40mg	Merck Sharpe & Dohme Ltd

Note: Testim although still licensed for use is no longer marketed by Ferring Pharmaceuticals in the UK
https://www.prescriber.org.uk/2018/01/notice-of-testim-discontinuation

Table 2. NHS list price for testosterone products available in the UK [3,4]

Drug Name	Manufacturer	Size	Unit	NHS indicative price
Testogel® 50mg/5g gel sachets	**Besins Healthcare (UK) Ltd**	**30**	**Sachets**	**£31.11**
Testogel® 16.2mg/g gel pump	**Besins Healthcare (UK) Ltd**	**88**	**Grams**	**£31.11**
Tostran® 20mg/g gel pump	**Kyowa Kirin Ltd**	**60**	**Grams**	**£28.63**
Testavan® 20mg/g gel pump	**Ferring Pharmaceuticals Ltd**	**85.5**	**Grams**	**£25.22**
Nebido® 1000mg/4ml	**Bayer HealthCare**	**1**	**Vial**	**£87.11**
Sustanon® 250mg/1ml	**Aspen Pharma Trading Ltd**	**1**	**Ampoule**	**£2.45**
Testosterone enantate 250mg/1ml	**Alliance Pharmaceuticals**	**3**	**Ampoules**	**£87.73**
Restandol Testocaps® 40mg	**Merck Sharpe & Dohme Ltd**	**30**	**Capsules**	**£8.55**

Note: Testim although still licensed for use is no longer marketed by Ferring Pharmaceuticals in the UK
https://www.prescriber.org.uk/2018/01/notice-of-testim-discontinuation

3. MIMS Online: Accessed June 2019
4. NHS Business Services Authority https://apps.nhsbsa.nhs.uk/DMDBrowser/DMDBrowser.do Accessed June 2019

Table 3. Dosage and frequency of testosterone products in the UK [3,4]

Drug Name	Recommended Dosing
Testogel® 50mg/5g gel sachets	Apply 50 mg transdermally, once daily; increased in steps of 25 mg, adjusted according to response; maximum 100 mg per day
Testogel® 16.2mg/g gel pump	Apply 40.5 mg transdermally, once daily; increased in steps of 20.25 mg, adjusted according to response; maximum 81 mg per day.
Tostran® 20mg/g gel pump	Apply 60 mg transdermally, once daily, subsequent application adjusted according to response; maximum 80 mg per day.
Testavan® 20mg/g gel pump	Apply 23 mg transdermally, once daily; increased in steps of 23 mg, adjusted according to response; maximum 69 mg per day
Nebido® 1000mg/4ml	1g by very slow deep intramuscular (IM) injection into gluteal muscle every 10—14 weeks. Adjust subsequent injection intervals according to serum testosterone levels.
Sustanon® 250mg/1ml	Initially, 250mg by slow intramuscular (IM) injection every 2—3 weeks. Maintenance, 250mg by IM injection every 3—6 weeks according to response.
Testosterone enantate 250mg/1ml	1ml by deep intramuscular (IM) injection every three weeks.
Restandol Testocaps® 40mg	Initially 3—4 oral capsules daily for two to three weeks, adjusting to 1—3 oral capsules daily according to response.

Note: Testim although still licensed for use is no longer marketed by Ferring Pharmaceuticals in the UK
https://www.prescriber.org.uk/2018/01/notice-of-testim-discontinuation

3. MIMS Online: Accessed June 2019
4. NHS Business Services Authority https://apps.nhsbsa.nhs.uk/DMDBrowser/DMDBrowser.do Accessed June 2019

References

1. Testogel Summary of Product Characteristics, Besins Healthcare, Aug 2018 https://www.medicines.org.uk/emc/product/6808/smpc Accessed July 2019
2. Wang C et al. J Clin Endocrinol Metab 2000;85:964-969
3. MIMS Online: Accessed June 2019
4. NHS Business Services Authority https://apps.nhsbsa.nhs.uk/DMDBrowser/DMDBrowser.do Accessed June 2019
5. Hackett G, et al. J Sex Med 2017;14:1504-23.
6. Dohle GR, et al. Guidelines of Male Hypogonadism. European Association of Urology 2015. Available at: uroweb.org/wp-content/uploads/18-Male-Hypogonadism_LR1.pdf Accessed May 2019
7. Mulhall JP, et al. American Urological Association 2018.
8. Bhasin S, et al. J Clin Endocrinol Metab 2018;103(5):1715-44.
9. Garvey TW, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for Comprehensive Medical Care of Patients with Obesity. Available at: aace.com/files/guidelines/ObesityExecutiveSummary.pdf Accessed May 2019
10. American Diabetes Association. Diabetes Care 2019;42(Suppl.1):S34–S45. Available at: care.diabetesjournals.org/content/diacare/suppl/2018/12/17/42.Supplement_1.DC1/DC_42_S1_Combined_FINAL.pdf Accessed May 2019.
11. Hackett, G et al. J Sex Med. 2018 Apr;15(4):430-457
12. Lunenfeld et al Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men Aging Male, 2015; 18(1): 5–15
13. Swerdloff R et al. J Clin Endocrinol Metab 2000;**85**:4500-4510
14. Wang C et al. J Clin Endocrinol Metab 2004;**89**:2085-2098
15. Behre HM et al. J Aging Male 2012;**15(4)**: 198-207