Drugs & Therapy Perspectives
https://doi.org/10.1007/s40267-019-00627-7

ADIS DRUG Q&A

Testosterone 2% gel (Testavan®, Testarzon®) in adult male hypogonadism: a profile of its use

Katherine A. Lyseng-Williamson[1]

Abstract

Testosterone 2% (20 m/mL) transdermal gel (Testavan®, Testarzon®), is indicated to treat adult male hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests. It is applied once daily using a hands-free applicator, with an initial recommended daily dosage equivalent to 23 mg testosterone, which may be increased to 46 or 69 mg/day. In clinical studies, once-daily application of Testavan 2% gel was associated with rapid and extensive absorption of testosterone, leading to normalization of testosterone levels in hypogonadal men. After application, testosterone levels achieve their peak in ≈ 2–4 h, then decrease to pre-application levels at ≈ 12 h, broadly mirroring the natural diurnal rhythm of male testosterone. Testavan 2% gel also improved sexual, physical and mental functioning, fatigue and health-related quality of life. The components of Testavan's novel gel enhance the transdermal transfer of testosterone into the blood, allowing the application of lower doses of testosterone in smaller gel volumes relative to the application of other transdermal testosterone gels. Testavan 2% gel is applied using the applicator cap rather than by hand, reducing the potential risk of secondary transfer of testosterone.

Adis evaluation of testosterone 2% gel (Testavan®, Testarzon®) in the treatment of adult male hypogonadism
Novel transdermal gel enhances the bioavailability of testosterone, resulting in the application of relatively low testosterone doses in small gel volumes
Normalizes plasma testosterone levels, with a pattern of testosterone peaks and nadirs in keeping with the natural diurnal rhythm of male testosterone
Provides rapid and sustained improvements in sexual, physical and mental functioning, fatigue, overall health-related quality of life and other patient-reported outcomes
Reduces the potential risk of secondary transfer through the use of the simple hands-free applicator

What is the rationale for developing Testavan® 2% gel?

Male hypogonadism is characterized by levels of serum testosterone that are lower than normal (i.e. < 300 ng/dL), as well as clinical symptoms of testosterone deficiency, such as low libido, erectile dysfunction, increased body fat, decreased muscle mass and bone mineral density and depressed mood [1–4]. Importantly, a diagnosis of hypogonadism requires both clinical and biochemical evidence of low testosterone levels. In men with hypogonadism due to insufficient secretion of endogenous testosterone, treatment with exogenous testosterone restores testosterone levels to within the normal range. Over time, the normalization of serum testosterone leads to improvements in the clinical symptoms of hypogonadism, including sexual desire and function (e.g. sexual performance and the number of spontaneous erections), as well as improvements in health-related quality of life (HR-QOL) [1–4].

A variety of testosterone formulations with broadly similar effectiveness, but different routes of administration and pharmacological and tolerability profiles, are available to treat men with hypogonadism [1, 3, 4]. When taken orally, testosterone is poorly absorbed, rapidly metabolized and inactivated by the liver, leading to poor bioavailability and

✉ Katherine A. Lyseng-Williamson
dtp@adis.com

[1] Springer, Private Bag 65901, Mairangi Bay 0754, Auckland, New Zealand

Published online: 10 April 2019

the need for relatively large dosages [5]. Formulations that use other methods of administration of testosterone, therefore, have been developed, including intramuscular injections, buccal patches, transdermal patches and, most recently topical gels, solutions and nasal sprays [4, 6, 7].

When delivered transdermally, controlled amounts of testosterone are absorbed directly into the bloodstream [4, 6, 7]. Of the transdermal formulations of testosterone, testosterone gels are the most commonly used due to their overall favourable efficacy and tolerability profiles, ease of application and dose titration, and the number of marketed formulations [6, 7]. When gels are applied by hand, however, there is a potential risk of secondary transfer of testosterone to other individuals, including children and women, which increases their respective risk of premature puberty and virilisation [3, 4, 7]. There remains, therefore, a need for new transdermal testosterone formulations that further enhance the absorption and bioavailability of testosterone, are easy and convenient to use, and minimize the risk of secondary transfer [6].

Advances in transdermal delivery have led to the development a testosterone 2% gel (Testavan®, Testarzon®) [8] that enhances the absorption of testosterone, allowing a lower dose of testosterone to be applied in a relatively small volume of gel. This article reviews the characteristics, clinical use, efficacy and tolerability of this novel transdermal testosterone 2% gel (hereafter referred to as Testavan to avoid confusion with other marketed testosterone gels).

What are the characteristics of Testavan 2% gel?

Novel topical vehicle

The vehicle used to deliver testosterone via Testavan 2% gel is a novel hydro-alcoholic, highly viscous, transparent and non-staining topical gel [6, 8, 9]. The gel contains a unique combination of [9]:

- *Non-volatile solvents* Delay the crystallization of drugs, thereby allowing the molecular form of drugs to permeate into the skin.
- *Permeation enhancers* Work together with the solvents to temporarily disturb skin permeability, thereby allowing rapid absorption of drugs through the skin.
- *Volatile solvents* Fluidize intercellular skin lipids, thereby enabling rapid and extensive absorption of drugs into the blood.

Exposure to testosterone

The pharmacodynamic profile of testosterone applied via Testavan 2% gel is consistent with that of the endogenous androgens testosterone and dihydrotestosterone (DHT) [8]. Initial and subsequent doses of testosterone applied transdermally with Testavan 2% gel are relatively low, due to the bioavailability provided by the gel delivery system [6, 10, 11]. The approved dosages of Testavan 2% gel (Table 1) [8] were based on the exposure to testosterone in two open-label, phase 2 studies in hypogonadal men [10]. In these dose-escalation studies, 1.25, 2.50 and 3.75 mL of Testavan 2% gel (equivalent to 23, 46 and 70 mg of testosterone, respectively) were applied once daily by hand × 10 days (Study 1; $n = 20$), or by hand or applicator × 7 days (Study 2; $n = 20$). In both studies, exposure to total testosterone, free testosterone and DHT were dose proportional, leading to a recommended starting daily dosage for Testavan 2% gel of 23 mg of testosterone, with up-titration to 46 and 69 mg/day if required [10].

The bioavailability of testosterone is significantly higher with Testavan 2% gel than with Testogel® (Androgel®) 1% [11]. An open-label cross-over study in healthy men who had undergone pharmacological suppression of endogenous testosterone compared the relative bioavailability of 50 mg of testosterone administered transdermally via 5 g of Testavan 1% gel, 2.5 g of Testavan 2% gel, and 5 g of Testogel 1% (all gels were administered once daily for 7 days, with a 6–9 day washout period) [11]. Testavan 1 and 2% gel provided 2.63- and 1.61-fold higher testosterone bioavailability than Testogel 1% on day 1 ($p \leq 0.001$), and 2.00- and 1.39-fold higher testosterone bioavailability on day 7 ($p \leq 0.05$). The mean times to maximum levels (t_{max}) of serum testosterone were shorter with Testavan 1 and 2% gel (≈5–6 h on days 1 and 7) than with Testogel 1% (≈20 h on day 1 and ≈13 h without a marked value on day 7); corresponding maximum serum levels were higher with Testavan 1 and 2% gel than with Testogel 1% on day 1 (6.25 and 2.97 vs 1.71 ng/mL) and day 7 (6.67 and 3.16 vs 2.22 ng/mL). As a result of enhanced bioavailability of testosterone provided bythe Testavan gel delivery system, the applied dose of testosterone is lower with Testavan 2% gel than with Testogel 1% gel (e.g. initial applied dose 23 vs 50 mg; maximum applied dose 69 vs 100 mg) [8, 12].

Application

Testavan 2% gel provides a hands-free method of applying transdermal testosterone (Fig. 1; Table 1) [8]. In a dose-escalation study 2 [10], the method of application (by hand or using the applicator) did not affect exposure to testosterone or DHT to a significant extent. Importantly, most patients were satisfied with the use of the applicator. Of the 18 study completers, 15 (83%) preferred applying the gel using the applicator over applying the gel by hand, 13 (72%) found the applicator easy to use, and 12 (67%) found the applicator more convenient to use than application by hand [10].

Table 1 Summary of the application and use of Testavan® 2% gel) in the treatment of adult male hypogonadism in the EU [8]

What is the approved indication for Testavan 2% gel?	
Testosterone replacement therapy for adult male hypogonadism, when testosterone deficiency has been confirmed by clinical features (e.g. regression of secondary sexual characteristics, changes in body composition, asthenia, reduced libido, erectile dysfunction, etc.) and biochemical tests (e.g. two separate blood testosterone measurements)	
How is Testavan 2% gel available?	
Multiple-dose hands-free pump applicator (Fig. 1) containing 85.5 g of testosterone 20 mg/g gel (equivalent to 56 metered applications)	
Each pump press delivers 23 mg of testosterone in 1.25 mL of gel	
How should Testavan 2% gel be used?	
Initial dosage	23 mg testosterone (1 pump press) applied once daily
Adjust dosage based on serum testosterone levels (also consider clinical signs/symptoms related to testosterone deficiency)	Measure serum testosterone 2–4 h after application ≈ 14 and 35 days after starting treatment or after a dosage adjustment
	Serum testosterone < 17.3 nmol/L (500 ng/dL): increase daily dose by 1 pump press (maximum 3 pump presses; equivalent to 69 mg testosterone)
	Serum testosterone > 36.4 nmol/L (1050 ng/dL): decrease daily dose by 1 pump press
Timing of application	At the same time each day, preferably in the morning
Apply using the hands-free applicator pump	Apply gel to clean, dry, intact skin on the upper arm/shoulder
	Spread the gel evenly across the maximum surface area of upper arm/shoulder using the applicator; ensure gel does not get onto the hands
Applying > 1 pump of gel	Actuate pump once and apply, then repeat pump press and application
	2 pumps (46 mg testosterone): apply 1st pump press to an upper arm/shoulder; apply 2nd pump press to opposite upper arm/shoulder
	3 pumps (69 mg testosterone): apply 1st pump press to an upper arm/shoulder; apply 2nd pump press to opposite upper arm/shoulder; apply 3rd pump press to initial upper arm/shoulder
What should be done after applying Testavan 2% gel?	
Clean applicator with tissue (discard safely) and replace the protective lid	
If gel has got onto hands during application, immediately wash with soap + water	
Let application site completely dry before getting dressed; avoid fire, flame or smoking until the gel is dry (alcohol in gel is flammable); minimize the use of body lotions and sunscreens at and just after application (lack of interaction studies with Testavan)	
Wait ≥ 2 h before showering, bathing or swimming	
How should secondary transfer of testosterone via close skin-to-skin contact be avoided?	
Advise patient to wear clothing that covers the application site at all times; wear a T-shirt over the application site during contact with partner or children; shower prior to foreseen skin-to-skin contact	
Avoid use in men with a major risk of noncompliance with safety instructions (e.g. men with severe alcoholism, drug abuse, severe psychiatric disorders)	
Wash the contact area with soap + water as soon as possible if a non-patient has contact with an uncovered/unwashed application area	
Pregnant and breast-feeding women must strictly avoid any contact with uncovered/unwashed application sites	
What are the monitoring requirements during longer-term treatment with Testavan 2% gel?	
Monitor testosterone levels at regular intervals; adjust dosage to ensure eugonadal testosterone levels are maintained	
Monitor for clinical symptoms of excessive androgen exposure (e.g. irritability, nervousness, weight gain, prolonged/frequent erections); decrease dosage as necessary	
Monitor haemoglobin levels, perform haematocrit and liver function tests, and measure lipid levels	

Testavan 2% gel is applied to the upper arm/shoulder (Table 1) [8], as application to this site is associated with better absorption of testosterone than application to the thigh or abdomen [10]. Dose-escalation study 1 evaluated the bioavailability of a single application of 2.5 mL of Testavan 2% gel (46 mg of testosterone) when applied by hand to three application sites (thigh, abdomen and upper arm/shoulder). Mean serum levels of total and free testosterone were significantly ($p < 0.05$) affected by the site of application, with levels being highest with application to the upper arm/shoulder, followed by application to the thigh and then to the abdomen [10].

How should Testavan 2% gel be used?

Testavan 2% gel is indicated as testosterone replacement therapy for adult male hypogonadism (Table 1) [8]. As with other testosterone replacement therapies, treatment with Testavan should be initiated only when testosterone

Fig. 1 Testovan® 2% gel hands-free applicator (reproduced with permission of Ferring Pharmaceuticals Ltd)

deficiency has been confirmed by the presence of clinical features and the results of biochemical tests (Table 1) [8]. It should not be used to treat male sterility or impotence, males aged < 18 years, or women of any age [8].

Testavan is applied once daily to the upper arm/shoulder using the cap applicator, with an initial dosage of 23 mg of testosterone (Table 1) [8]. Serum testosterone levels should be measured during initial therapy, with dosage adjustments to 46 or 69 mg of testosterone once daily to ensure testosterone levels in the normal range are achieved, then monitored regularly during treatment to ensure normal levels are maintained (Table 1) [8].

Precautions must be taken to avoid accidental secondary transfer of testosterone via skin-to-skin contact with other individuals (e.g. sexual partner and children) or pets (Table 1) [8]. Testavan 2% gel should be stored out of the reach and sight of children. Tissues used in the cleaning process and empty, partially used or unwanted applicators must be disposed of safely in accordance with local requirements [8].

What is the efficacy of Testavan 2% gel in men with hypogonadism?

The pharmacological, efficacy and tolerability profiles of Testavan 2% gel as testosterone replacement in men with hypogonadism has been demonstrated in three open-label, single arm, multicentre phase 3 studies [13, 14]. The initial study was conducted in Canada and the USA, and investigated the use of Testavan 2% gel at an initial testosterone dosage of 46 mg/day × 3 months, followed by a 6-month extension study, for a total treatment duration of 9 months [13]. Based on the results of these studies, the pivotal US study investigated the use of Testavan 2% gel at an initial testosterone dosage of 23 mg/day × 3 months [14]. The dosage of testosterone could be up-titrated [13, 14] and/or down-titrated [13] based on serum testosterone levels.

The studies enrolled men (aged 18–75 years) with hypogonadism who had serum testosterone values < 300 ng/dL on two separate occasions at least 3 days apart + clinical symptoms of testosterone deficiency, as assessed by the Androgen Deficiency in the Aging Male (ADAM) questionnaire [13, 14]. Among the key exclusion criteria were recent previous use of testosterone products [13, 14], urinary [13] or cardiovascular disease [13, 14], prostate cancer/suspected prostate malignancy [14] or palpable prostatic masses [13], body mass index < 18 or > 35 kg/m^2 [14], skin inflammation or disease [14], untreated sleep apnoea [14], haemoglobin A_{1c} > 9.0% [14], and abnormal liver function, haematocrit or creatinine levels [13].

At baseline in the three studies, most patients were Caucasian (77–78%) and aged ≤ 65 years (80–87%; mean patient age 54–57 years) [13, 14]. At baseline in the pivotal study, 96.2% of men had secondary hypogonadism, and the most common co-morbid conditions were hypertension, hypercholesterolaemia and type 2 diabetes (45.9, 25.2 and 20.1% of men, respectively) [14].

In the pivotal study [14], 160 enrolled patients started treatment with Testavan 2% gel at the approved testosterone dosage of 23 mg/day, with dosage increases to 46 mg/day, then a further increase to the maximum approved dosage of 69 mg/day if 4-h post-application serum total testosterone levels were outside the target of 500–1050 ng/dL on days 14, 35 and 56. At day 90, 5 men were still receiving Testavan 23 mg/day, whereas 45 had been up-titrated to 46 mg/day, and 89 had undergone further up-titration to 69 mg/day. At the end of the study, 159 men comprised the intent-to-treat (ITT) and safety population, and 155 comprised the full-analysis set (FAS), including 139 (87.4%) who completed the study without protocol violation (FAS completers) [14].

In the initial study [13], 180 (ITT and safety populations) patients started treatment with 46 mg/day, with 5 men being down-titrated to 23 mg/day, and 155 were up-titrated

to 69 mg/day. Of the 172 men who completed the initial 3-month study, 145 enrolled in the extension study. They continued treatment with their previous dosage or were down-titrated by 23 mg/day (i.e. 1 pump press) to 23 or 46 mg/day based on their testosterone level at the beginning of the 6-month extension; 127 men completed the study, with 110 in the FAS.

Changes in testosterone levels

At day 90 of the pivotal study [14], pharmacokinetic evaluations were conducted over a 24-h period (at 0, 2, 4, 6, 8, 10, 12, 18 and 24 h) in the FAS completers (5, 45 and 89 of who were receiving Testavan 2% gel at a testosterone dosage of 23, 46 or 69 mg/day, respectively).

The pharmacokinetic pattern of testosterone applied via the Testavan 2% gel applicator (i.e. rapid absorption with a peak ≈ 2–4 h after application, then a decrease to pre-application values at ≈ 12 h) broadly mirrors the natural diurnal rhythm of testosterone in men [14]. With all dosages of testosterone in the pivotal study, mean serum testosterone levels steeply increased 2 h after administration, followed by a gradual decline to near baseline levels. Serum DHT levels followed a broadly similar pattern, with levels increasing up to 4 h, then gradually declining to near baseline levels. Ratios of DHT to testosterone were consistent regardless of testosterone dosage at all timepoints over a 24-h period, with mean ratios of 0.12–0.24 with testosterone 23 mg and 0.12–0.23 with both testosterone 46 and 69 mg [14].

Dosage adjustments of Testavan 2% gel based on monitored serum testosterone levels provided mean testosterone levels within the normal physiological range by or before the end of the pivotal study (Fig. 2) [14]. Overall, mean and maximum levels of serum testosterone were somewhat lower with Testavan 2% gel at a testosterone dosage of 23 mg/day than with 46 and 69 mg/day, and generally comparable between 46 and 69 mg/day, with mean minimum levels being consistent across all dosages. (Fig. 2) [14]. Broadly similar exposure to serum testosterone was shown on day 90 in the initial study and at month 9 in the extension study [13].

In the pivotal study [14], generally consistent median t_{max} values of serum testosterone were found across all dosages (2.0–2.15 h at all timepoints), with the exception of a median value of 4.0 h at day 90 in 5 patients receiving testosterone 23 mg/day [14]. Median testosterone t_{max} was 4.0 h with testosterone 23 mg/day, and 2.0 h with both 46 and 69 mg/day,

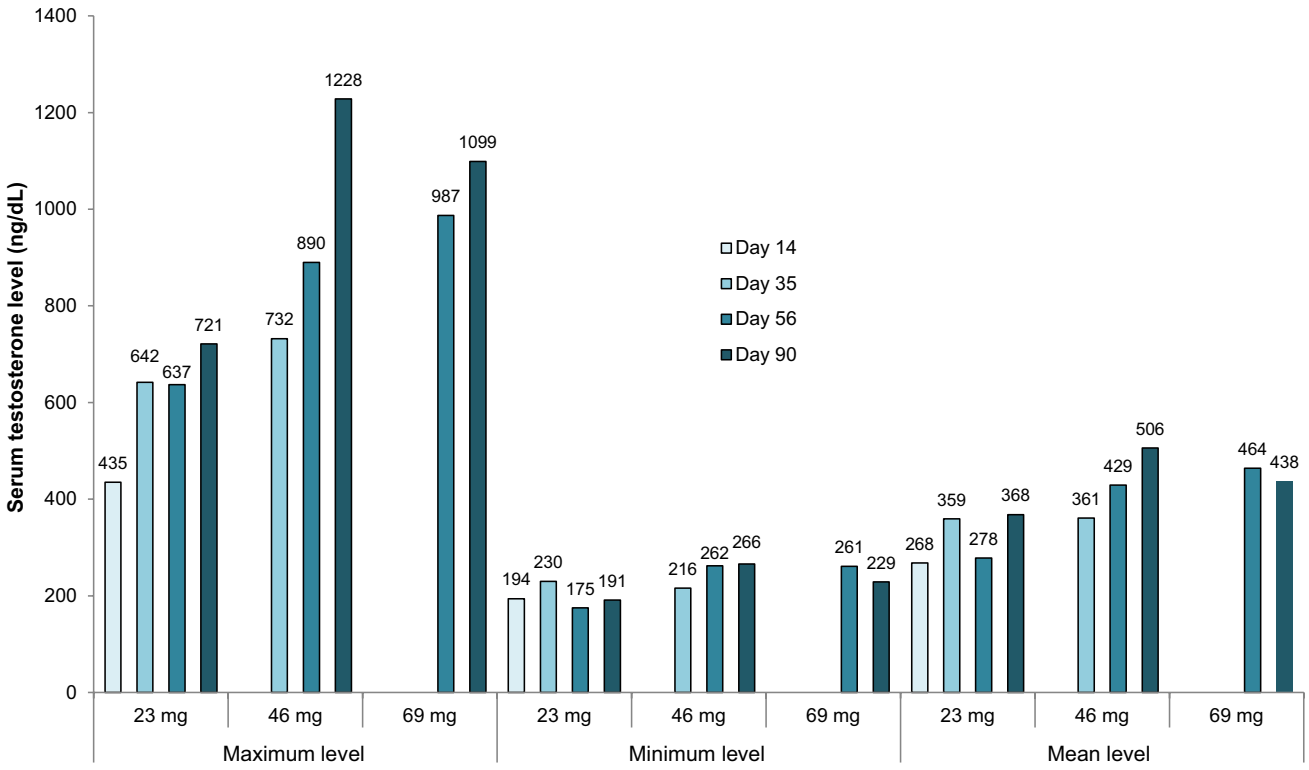

Fig. 2 Mean maximum, minimum and mean serum testosterone levels following treatment with Testavan® 2% gel in the pivotal clinical study in 160 men with hypogonadism [14]. All men received Testavan 2% gel at an initial testosterone dosage of 23 mg/day, with the dosage being up-titrated to 46 mg/day on days 14, 35 or 56, and to 69 mg/day on days 35 and 56, if required based on 4-h post-application serum total testosterone levels

as well as across all dosages in the initial study [13]. In the extension study, median testosterone t_{max} was 3.1, 2.1 and 4.0 h with testosterone 23, 46 and 69 mg/day, respectively (4.0 h across all dosages) [13].

Primary endpoint: testosterone response

Treatment with Testavan 2% gel provided a rapid and sustained testosterone response (defined as an average steady-state serum total testosterone within the physiological target range of 300–1050 ng/dL on day 90) in men with hypogonadism (Table 2) [13, 14]. In the pivotal study [14], treatment with Testavan 2% gel at a testosterone dosage of 23 mg/day was associated with a testosterone response in 29.1% of men at day 14, which increased to 75% at day 56, and was sustained at 76% at day 90 (Table 2) [14].

In the initial study that used Testavan 2% gel at a testosterone dosage of 46 mg/day [13], 52.8% achieved a response as early as day 1 post-dose, with 85.5% having a response at day 90. This rate was consistent with that after a total of 9 months of treatment (82.1%) at the end of the extension study [13].

Clinical outcomes

Clinical outcomes in men with hypogonadism improved as early as day 35 of Testavan 2% gel treatment, with further improvements during treatment for up to 9 months [13, 14]. At all timepoints (day 35, day 90 and 9 months), treatment with Testavan 2% gel was associated with significant improvements from baseline in:

- *Sexual function* As assessed by total and IIEF domain scores, all aspects of sexual function significantly improved relative to baseline ($p < 0.0001$; Table 2) [13,

Table 2 Efficacy of Testavan® 2% gel as testosterone replacement therapy in men with hypogonadism in open-label, single-arm phase 3 studies

Parameter	Pivotal study (starting dose testosterone 23 mg/day)[a] [14]		Initial study and its extension (starting dose testosterone 46 mg/day)[b] [13]	
	Day 35	Day 90	Day 90	9 months
Primary endpoint				
No. of evaluable men		155	172	110
% of men with a testosterone response[c] [95% CI]		76.1 [69.4–82.8]	85.5 [80.2–90.7]	82.1 [74.3–89.3]
Secondary clinical outcomes				
No. of evaluable men	146	139	172	127
Mean improvement (increase) from baseline in International Index of Erectile Function domain scores				
Total score			13.8*	17.5*
Erectile function	3.4*	4.9*	5.2*	6.7*
Intercourse satisfaction	1.3*	2.4*	2.8*	3.6*
Orgasmic function	1.3*	1.8*	1.7*	2.2*
Sexual desire	1.2*	2.2*	2.1*	2.4*
Overall satisfaction	1.2*	2.1*	2.1*	2.6*
Mean improvement (decrease) from baseline in Multidimensional Assessment of Fatigue domain scores				
Global fatigue index	−8.2*	−11.8*	−15.6*	−12.6*
Severity	−3.6*	−5.2*	−5.3*	−5.7*
Distress	−1.7*	−2.2*	−2.0*	−2.2*
Degree of interference in activities of daily living	−13.6 *	−16.7*	−18.9*	−22.9*
Timing	−2.6*	−3.0*	−2.8*	−2.9*
Mean improvement (increase) from baseline in Short Form-12 Health Survey scores				
Total physical component summary	1.2*	1.7*	NR*	NR*
Total mental component summary	6.7*	6.8*	NR*	NR*

NR numerical value for change from baseline not reported

*$p < 0.0001$ vs baseline

[a]The testosterone dose could be up-titrated to 46 mg/day at days 14, 35 or 56, then up to 69 mg/day on days 35 and 56, based on 4-h post-dose serum total testosterone levels. Results are reported for the full analysis set

[b]The testosterone dose could be up-titrated to 69 mg/day or down-titrated to 23 mg/day at days 21 and 56 based on morning pre-dose testosterone levels on day 14 and 49. Primary outcome results are in the full-analysis set; other results are in the intent-to-treat population

[c]Defined as an average steady-state serum total testosterone within the physiological target of 300–1050 ng/dL on day 90

14]. In addition, the severity and symptoms of low testosterone as assessed by ADAM questionnaire scores significantly improved in 44% of men in the initial study [13].

- *Fatigue* As assessed by the Multidimensional Assessment of Fatigue global and domain scores, men had significantly less overall fatigue, including less severe fatigue, less distress and lower fatigue-related interference in performing the activities of daily living than at baseline ($p < 0.0001$; Table 2) [13, 14].
- *HR-QOL* As assessed by Short Form-12 Health Survey scores, overall physical and mental HR-QOL improved to a significant extent from baseline ($p < 0.0001$; Table 2) [13, 14]. Scores for the individual domains of the mental component (i.e. mental health, vitality, role-emotional and social functioning) also significantly ($p < 0.0001$) improved from baseline at all timepoints [13, 14]. Individual domain scores of the physical component (i.e. general health, physical functioning, role-physical and bodily pain) also significantly ($p < 0.05$) improved [13, 14], with the exception of bodily pain at day 90 in the pivotal study ($p = 0.06$) [14].

Treatment satisfaction

Patients were satisfied with the use of Testavan 2% gel, according to patient responses to a treatment satisfaction questionnaire in the pivotal study [14].

- *Satisfaction with the hands-free cap applicator* 93.5% of men were very satisfied/satisfied.
- *Ease of use of applicator* 93.5% of men found if very easy to use.
- *Risk of secondary transfer of testosterone* 87% of men felt that Testavan 2% gel lowered the risk of transfer of testosterone to child/partner through direct contact with application site or hands.

What is the tolerability profile of Testavan 2% gel?

The tolerability profile of exogenous testosterone is well established [6, 15]. According to the review comparing Testavan 2% gel with other topical testosterone formulations [6], the most common adverse events across all formulations are acne, headache, emotional lability, nervousness, abnormal dreams and gynecomastia, all of which were reported in < 8% of recipients.

Testavan had an overall tolerability profile consistent with those of other testosterone gels, with adverse effects that are in keeping with exogenous testosterone administered in a transdermal formulation [6]. In the safety populations of the three open-label phase 3 studies ($n = 159$ in pivotal study [14], and 180 and 145 in the initial study and its extension [13]), 34.0, 34.4 and 19.3% of Testavan 2% gel recipients, respectively, reported at least one treatment-emergent adverse event, and 4.4, 0.6 and 1.4% withdrew from treatment because of a tolerability issue [13, 14]. Adverse events considered to be related to treatment were limited to 22 of 95 adverse events in 62 men in the initial study, and 14 of 49 adverse events in 28 men in the extension study [13].

In men treated with Testavan 2% gel for up to 9 months in phase 2 and 3 studies, adverse events with a suspected relationship to treatment that were reported in ≥ 0.1 to < 10% of patients were limited to the following [8]:

- *Application site reactions* Includes rash, erythema, pruritus, dermatitis, dryness and skin irritation [8]. Most common type of adverse effect (reported in 4% of patients), with most being of mild to moderate severity [8]. In the pivotal study, eight men reported mild-to-moderate applicate site reactions, with two discontinuing treatment [14]. Such reactions may be caused by the presence of propylene glycol and/or ethanol in the gel [8]. The use of Testavan is contraindicated in men with known hypersensitivity to propylene glycol or any other gel excipient (e.g. ethanol, diethylene glycol monoethyl ether, Carbomer 980, trolamine, disodium edetate). If a severe application site reaction occurs, treatment with Testavan 2% gel should be reviewed and discontinued if necessary [8].
- *Hypertension* Reported in 1.4% of men in the pivotal study [14]. Testosterone should be used with caution in patients with underlying hypertension (Table 3) [8].
- *Increased prostatic specific antigen (PSA) levels* PSA levels > 0.1 nmol/L (> 4 ng/mL) were reported at various timepoints in a total of 7 of the 339 men in the phase 3 studies [4 men (1.3%) in the pivotal study [14] + 3 men (1.7%) in the initial study and its extension [13]. The mean change from baseline in PSA levels was 0.008 nmol/L [6]; retested values were < 0.1 nmol/L for the remainder of the pivotal study [14]. Current data are inconclusive with regard to a potential link between exogenous testosterone treatment and an increased risk of prostate cancer [8]. Appropriate precautions should be followed in men with, or at risk, of prostate cancer (Table 3) [8].
- *Increased triglyceride levels/hypertriglyceridaemia* Increased blood triglyceride levels were reported in 1.9 and 2.2% of men in the pivotal [14] and initial study [13]), and hypertriglyceridaemia/hyperlipidaemia in 1.3% of men in the pivotal study [14]. Lipid levels should be monitored regularly (Table 3) [8].
- *Increased haematocrit and haemoglobin values.* Increases are due to the dose-dependent effect of exogenous testosterone on stimulating erythropoiesis [6]. In the

Table 3 Summary of selected precautions pertaining to the use of Testavan® 2% gel in the treatment of male hypogonadism in the EU [8]

What special precautions regarding breast or prostate cancer should be taken with Testavan 2% gel?
Contraindications: use is contraindicated in men with known or suspected breast or prostate carcinoma
Prior to initiating treatment: exclude risk of pre-existing prostate cancer
During treatment: using recommended methods, carefully monitor prostate gland (e.g. perform digital rectal examination and estimation of serum PSA levels) and breast at least once yearly (twice yearly in elderly men and those at risk due to clinical or familial factors)
Be aware that androgen therapy may accelerate progression of sub-clinical prostate cancer and benign prostatic hyperplasia
What special precautions regarding the risk of oedema should be taken with Testavan 2% gel?
Men with severe cardiac, hepatic or renal insufficiency or ischaemic heart disease: discontinue treatment immediately if severe complications characterized by oedema ± congestive heart failure occur
Concomitant testosterone + ACTH or corticosteroids: ↑ risk of oedema (particularly in men with cardiac, renal or hepatic disease)
What are some of the other situations in which the use of Testavan 2% gel requires caution?
Men with cancer at risk of hypercalcaemia/hypercalciuria due to bone metastases: monitor serum calcium levels regularly
Men with hypertension: testosterone may ↑ blood pressure (use with caution)
Men with thrombophilia: thrombotic events during testosterone treatment have been reported (use with caution)
Concomitant androgen + oral anticoagulant: anticoagulant effects may ↑; closely monitor INR especially when starting/stopping androgen
Men with ischaemic heart disease, epilepsy or migraine: testosterone treatment may aggravate these conditions (use with caution)
What laboratory values should be monitored during treatment?
Monitor haemoglobin levels, perform haematocrit and liver function tests, and measure lipid levels

ACTH adrenocorticotropic hormone, *INR* international normalized ratio, *PSA* prostatic specific antigen, ↑ increase

pivotal study, mean haematocrit slightly increased from a baseline value of 43.75–45.7 at day 120; men with high haematocrit and haemoglobin levels did not have high testosterone levels [14]. In extension study, increased haematocrit was reported in four men (2.8%), with two withdrawing from the study due to haematocrit > 54% [13]. Increased haemoglobin levels were reported in 1.1 and 1.4% of men in the initial study and its extension [13]. Haematocrit and haemoglobin should be monitored regularly (Table 3) [8].

- *Headache* Reported in 1.1% of patients in the initial study [13].

Precautions

As androgens have numerous effects throughout the body, testosterone treatment, including that with Testavan 2% gel, requires precautions in certain patient populations, and may affect the pharmacodynamic profile of some concomitant drugs (Table 3) [8]. The effects of Testavan on male fertility have not been investigated; however, based on animal studies, testosterone may reversibly suppress spermatogenesis in a dose-dependent manner due to inhibitory effects of exogenous testosterone on pituitary follicle stimulating hormone [8].

What is the current clinical position of Testavan 2% gel?

Testavan 2% gel is a novel transdermal gel for normalizing serum testosterone levels in adult males with hypogonadism. Overall, Testavan 2% gel normalized testosterone levels in > 75% of men, improved sexual, physical and mental functioning, reduced fatigue and improved HR-QOL in clinical studies in men with hypogonadism [13, 14]. Other transdermal testosterone gels provide comparable benefits [6, 12, 16, 17]; however, there are some differences between some of the properties of testosterone gels (Table 4) [8, 12, 16, 17]. The advantages and disadvantages of the available formulations of testosterone replacement therapy, together with patient preferences, should be taken into account when treating individuals with hypogonadism [1, 4].

Relative to other transdermal gels currently widely available in the EU [12, 16, 17], Testavan 2% gel [8] offers the following:

- *Low applied testosterone dosage* The properties of the novel vehicle gel enhance the transdermal transfer of testosterone into the blood [9], allowing applied testosterone dosages to be lower with Testavan 2% gel than with other testosterone gels (23 vs 50 or 60 mg/day as the initial applied dosage; 69 vs 80 or 100 mg/day as the maximum applied dosage; Table 4) [8, 12, 16, 17].
- *Mirroring of the natural diurnal rhythm of testosterone levels* Following application of Testavan 2% gel, testosterone is rapidly absorbed with a peak ≈ 2–4 h after application followed by a decrease to pre-application levels

Table 4 Differential features of transdermal testosterone gels approved for testosterone replacement in men with hypogonadism currently widely available in the EU

Parameter	Testavan® 2% [8]	Testim® 1% [16]	Testogel® 1% [12]	Tostran® 2% [17]
Other tradenames [18]	Testavance®		AndroGel®	Fortesta®, Fortigel®, Itnogen®, Tostrex®
Availability in the EU	Multiple-dose pump applicator; contains 85.5 g of testosterone 20 mg/g gel (56 pump presses)	Single-use tube; contains 50 mg of testosterone in 5 g of gel	Single-use sachets; contains 50 mg of testosterone in 5 g of gel	Multiple-dose pump container; contains 60 g of testosterone 20 mg/g gel (60 pump presses)
Year of first approval	2018	2009	2006	2006
Method of application	Cap applicator	By hand	By hand	By hand (1 finger)
Site of application	Upper arms and shoulders[b]	Upper arms and/or shoulders[b]	Both shoulders, both arms or abdomen	Abdomen or both inner thighs (rotate sites)
Post-application bathing/showering	After ≥ 2 h	After ≥ 6 h	After ≥ 6 h	After ≥ 2 h
Initial applied dose	23 mg	50 mg	50 mg	60 mg
Timing of dose titration after initiation	4 h post-application on days 14, 35 and 56	Before applying the next dose on day 7–14	Before applying the next dose on day 3–7	2 h post-application at ≈ 14 days
Dose titration if required	↑ to 46 mg, then to 69 mg	↑ to 100 mg	↑ to 75 mg, then to 100 mg	↑ to 80 mg
Amount of product per usual dose	23 mg: 1.25 mL (1.15 g; 1 pump press)	50 mg: 5 g (1 tube)	50 mg: 5 g (1 sachet)	60 mg: 3 g (6 pump presses)
	46 mg: 2.5 mL (2.30 g; 2 pump presses)	100 mg: 10 g (2 tubes)	75 mg: 7.5 g (1.5 sachets)	80 mg: 4 g (8 pump presses)
	69 mg: 3.75 mL (3.45 g; 3 pump presses)		100 mg: 10 g (2 sachets)	
Special storage conditions[a]	None	Not above 25 °C	None	Not above 25 °C; store canister upright

[a]All testosterone gels should be stored out of the sight and reach of children

[b]Use both upper arms/shoulder if treatment with more than 1 pump press or tube is required

at ≈ 12 h, which broadly follows the pattern of endogenous testosterone levels in men [13, 14].

- *Low application volume* The properties of the novel vehicle gel allows the amount of gel to be applied to lower with Testavan 2% gel than with other testosterone gels (1.15 vs 3–5 g/day as the initial dosage; 3.45 vs 10 g/day as the maximum dosage; Table 4) [8, 12, 16, 17], thereby ameliorating the potential risk of secondary transfer of unabsorbed testosterone [6].
- *Metered multiple-dose container* The Testavan 2% gel multiple-dose pump accurately measures each testosterone dose (1, 2 or 3 pump presses for testosterone doses of 23, 46, 69 mg). This may be more accurate and convenient than the use of single-use tubes or sachets or multiple-dose pump containers that require 6 or 8 pump presses (Table 4) [12, 16, 17].
- *Hands-free application* Unlike other transdermal testosterone gels which are applied by hand [12, 16, 17], Testavan [8] is applied with a cap applicator (Table 4), which also reduces the risk of secondary transfer [6]. Men with hypogonadism may prefer hands-free application, and have found the Testavan applicator to be satisfactory, convenient and easy to use [10, 14].
- *Quick-drying gel* Patients can bathe, shower or swim 2 h after-application of Testavan 2%, which is shorter than with some of the other gels (Table 4) [12, 16], which may be more convenient for patients.

Acknowledgements The manuscript was reviewed by: *S. Arver,* ANOVA-Andrology, Sexual Medicine and Trans Medicine, Karolinska University Hospital and the Karolinska Institute, Stockholm, Sweden; *F.A. Cadegiani,* Adrenal and Hypertension Unit, Division of Endocrinology and Metabolism, Department of Medicine, Universidade Federal de São Paulo, São Paulo, Brazil; *C.N. Jayasena,* Department of Investigative Medicine, Imperial College London, London, UK; *N. Karsiyakali,* Department of Urology, Çukurca State Hospital, Çukurca, Hakkâri, Turkey. During the peer review process, Ferring Pharmaceuticals Ltd, the marketing-authorization holder of Testavan, was also offered an opportunity to provide a scientific accuracy review of their data. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Compliance with ethical standards

Funding The preparation of this review was not supported by any external funding.

Conflicts of interest KA. Lyseng-Williamson is an employee of Adis/Springer, is responsible for the article content and declares no conflicts of interest.

References

1. Dohle GR, Arver S, Bettocchi C, et al. EAU guidelines on male hypogonadism. 2018. http://uroweb.org/guideline/male-hypogonadism/. Accessed 2019.
2. Morales A, Bebb RA, Manjoo P, et al. Diagnosis and management of testosterone deficiency syndrome in men: clinical practice guideline. CMAJ. 2015;187(18):1369–77.
3. Surampudi PN, Wang C, Swerdloff R. Hypogonadism in the aging male: diagnosis, potential benefits, and risk of testosterone replacement therapy. Int J Endocriol. 2012;2012:625434. https://doi.org/10.1155/2012/625434.
4. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. Clin Endocrinol Metab. 2018;103(5):1715–44.
5. Täuber U, Schröder K, Düsterberg B, et al. Absolute bioavailability of testosterone after oral administration of testosterone-undecanoate and testosterone. Eur J Drug Metab Pharmacokinet. 1986;11(2):145–9.
6. Arver S, Stief C, de la Rosette J, et al. A new 2% testosterone gel formulation: a comparison with currently available topical preparations. Andrology. 2018;6(3):396–407.
7. Ullah M, Riche DM, Koch CA. Transdermal testosterone replacement therapy in men. Drug Des Devel Ther. 2014;8:101–12.
8. Testavan® 20 mg/g transdermal gel: summary of product characteristics and patient leaflet. West Drayton: Ferring Pharmaceuticals; 2018.
9. Alberti I, Grenier A, Kraus H, et al. Pharmaceutical development and clinical effectiveness of a novel gel technology for transdermal drug delivery. Expert Opin Drug Deliv. 2005;2(5):935–50.
10. Efros M, Carrara D, Neijber A. The efficacy, bioavailability and safety of a novel hydroalcoholic testosterone gel 2% in hypogonadal men: results from phase II open-label studies. Andrologia. 2016;48(6):637–45.
11. Olsson H, Sandstrom R, Neijber A, et al. Pharmacokinetics and bioavailability of a new testosterone gel formulation in comparison to Testogel(R) in healthy men. Clin Pharmacol Drug Dev. 2014;3(5):358–64.
12. Testogel® 50 mg, gel in sachet: summary of product characteristics and patient leaflet. London: Besin Healthcare (UK) Ltd; 2018.
13. Belkoff L, Brock G, Carrara D, et al. Efficacy and safety of testosterone replacement gel for treating hypogonadism in men: phase III open-label studies. Andrologia. 2018;50(1):e12801.
14. Cunningham G, Belkoff L, Brock G, et al. Efficacy and safety of a new topical testosterone replacement gel therapy for the treatment of male hypogonadism. Endocr Pract. 2017;23(5):557–65.
15. Layton JB, Meier CR, Harpless JL, et al. Comparative safety of testosterone dosage forms. JAMA Intern Med. 2015;175:1187–96.
16. Testim® 50 mg transdermal gel: summary of product characteristics and patient leaflet. West Drayton: Ferring Pharmaceuticals; 2016.
17. Tostran® 2% gel: summary of product characteristics and patient leaflet. Galashiels: Kyowa Kirin Ltd; 2016 .
18. Adis Insight. Testosterone products for hypogonadism. https://adisinsight.springer.com/search. Accessed 20 Feb 2019.