

# A novel metered-dose 2% testosterone gel treatment for male hypogonadism

## Keywords

Aging  
Endocrinology  
Hypogonadism  
Testosterone  
Urology

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## Abstract

**Background:** Male hypogonadism arises from a deficiency in testosterone secretion that may occur naturally with increasing age, or as a result of malfunction of the hypothalamus, pituitary gland or testes. Tostran<sup>®</sup> (also known as Fortigel<sup>®</sup>, Itnogen<sup>®</sup> and Tostrex<sup>®</sup>) is a metered-dose gel formulation of 2% testosterone that was recently developed to treat male hypogonadism and to overcome the disadvantages exhibited by some testosterone formulations.

**Methods:** A prospective Phase II trial of Tostran in men with primary or secondary hypogonadism evaluating the effect of showering was conducted.

**Results:** This trial demonstrated that showering 2 h after application of Tostran has no significant effect on serum testosterone levels.

**Conclusion:** Market research in the UK and Germany has indicated that endocrinologists would consider switching patients to Tostran from other formulations, especially other gels. Their preference is due to the dosage and administration advantages of Tostran, the flexibility of the metered-dose formulation, and the ability to shower 2 h after application.

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## Testosterone replacement therapy with Tostran

Testosterone plays a pivotal role in physiological development, sexual function, reproduction, skin, bone and hair growth, and in the maintenance of muscle bulk, erythropoiesis, cholesterol and lipid levels, and secondary sexual characteristics [1]. Male hypogonadism is a result of the reduction or absence of secretion of testosterone, which may be either primary (as a result of testicular dysfunction) or secondary (pituitary failure or hypothalamic dysfunction leading to a decrease in the release of testosterone from the testes) [2]. Men with hypogonadism can experience reduced libido and sexual function, reductions in energy and body strength, changed physique, alterations in well-being and mood, diminished cognitive function and a reduced quality of life [3]. A decrease in testosterone levels is also associated with increased falls [4], insulin resistance, vascular risk, and risk of premature

mortality [5], and can have an adverse effect on multiple organ systems [3,6]. The prevalence of hypogonadism increases significantly with age (Figure 1) [7]. With an ageing population, the number of men requiring treatment for hypogonadism will increase considerably.

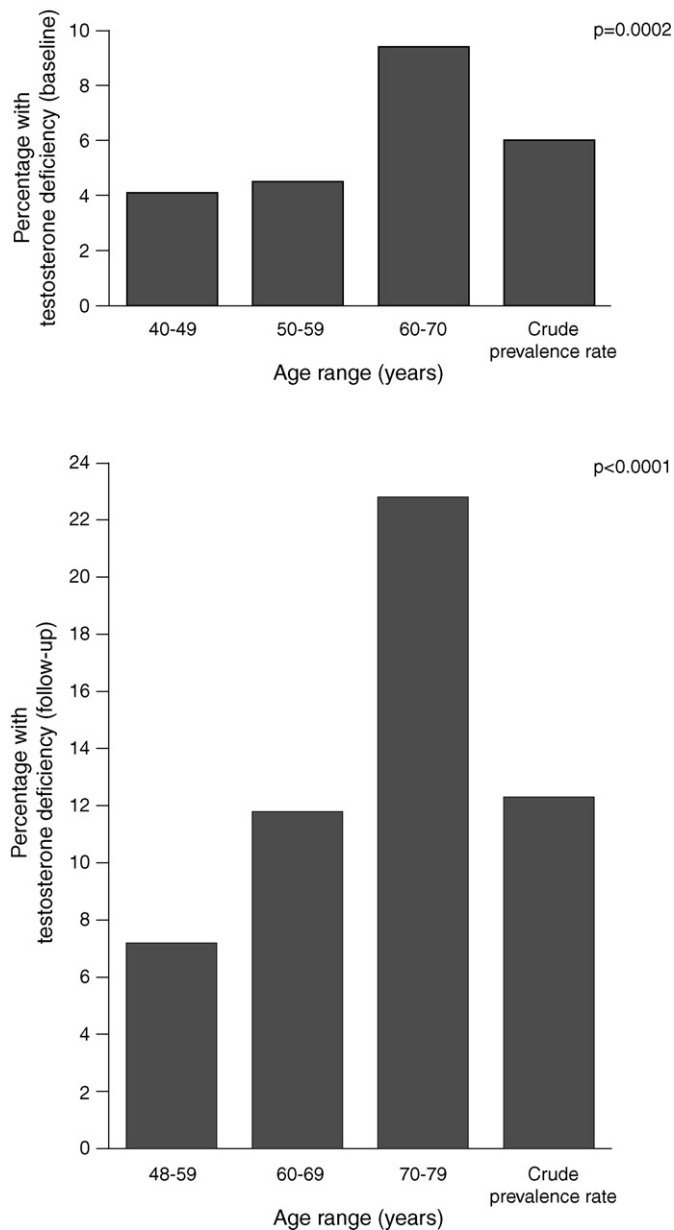
In addition, hypogonadism has been associated with increases in central obesity, cardiovascular risk, insulin levels and diabetes [8]. The prevalence of hypogonadism has been shown to be higher in men with hypertension (odds ratio (OR) = 1.84), hyperlipidaemia (OR = 1.47), diabetes (OR = 2.09) and obesity (OR = 2.38) [9].

The secretion of testosterone from the testes and adrenal glands is under hormonal control (Figure 2) [10]. In a healthy adult man the testes secrete approximately 95% (4–10 mg) of the total daily testosterone production, with the remainder being derived from androgens produced by the adrenal glands.

Male hypogonadism is managed by the replacement of testosterone. Clinical efficacy

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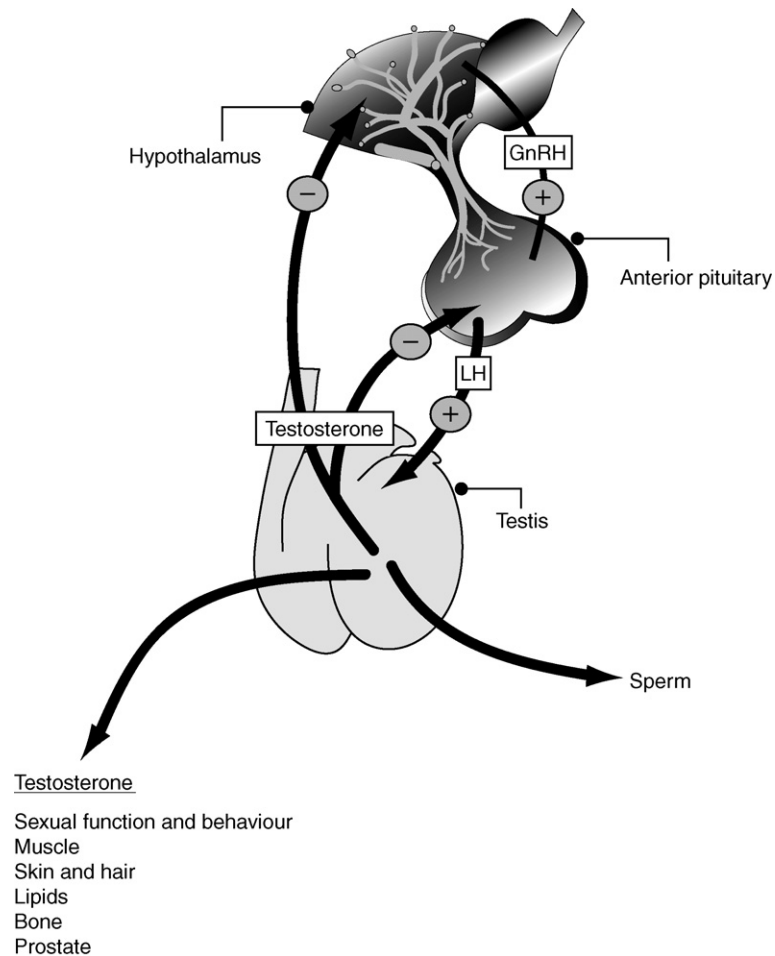
Online 3 December 2007



**Figure 1** Prevalence of testosterone deficiency syndrome in ageing men (baseline and after a mean of 8.8 years' follow-up). Men were considered to be testosterone deficient if they met one of the following two conditions: (1) at least three signs/symptoms and total testosterone less than 200 ng/dl (6.94 nmol/l); or (2) at least three signs/symptoms and total testosterone 200–400 ng/dl (6.94–13.88 nmol/l) and free testosterone less than 8.91 ng/dl (0.3092 nmol/l). *P* value calculated by testing the null hypothesis of no age trend in prevalence using the Cochran-Armitage test for trend. Adapted, with permission, from Araujo et al (2004) [7].

[11,12] and tolerability [11,13,14] of testosterone treatment is well established. In the 1930s and 1940s, intramuscular and implantable testosterone formulations were used to treat hypogonadism. A number of other formulations of testosterone are now available: oral, buccal, depot solution, subcutaneous implant and transdermal gels.

With oral administration of testosterone, frequent administration (2–3 times daily) is required and is associated with variable serum levels, gastrointestinal intolerance and hepatic toxicity [15]. Testosterone injections, with a frequency of injection of 1–4 weeks, are relatively inexpensive and widely available, but may result in rapid fluctuation of serum tes-



**Figure 2** Hormonal control of testosterone secretion. Adapted, with permission, from Bagatell & Bremner (1996) [10].

tosterone levels [16], with associated mood and/or energy swings and a risk of polycythaemia. Quarterly injections provide more predictable levels after an initial 6-week loading phase but require deep intramuscular injection and may be painful. A further limitation is the inability to rapidly discontinue therapy in the event of the development of a contraindication [3]. Transdermal patches have been shown to sustain normal testosterone levels and provide high serum dihydrotestosterone levels [17]. However, this formulation is associated with skin irritation in approximately one-third of patients, due to the presence of absorption enhancers [18].

Gel formulations result in stable serum testosterone levels within the normal range and are well tolerated, with infrequent, transient skin irritation and low discontinuation rates [19,20]. Dose titration is not facilitated by the sachets or tubes in which conventional 1% testosterone gel is supplied and wastage can occur if the whole unit is not required. Further-

more, daily application of relatively large volumes containing 5 or 10 g of 1% gel may limit patient acceptability, and hence compliance.

A novel metered-dose 2% transdermal testosterone gel, Tostran, has been developed to overcome some of the disadvantages of other available formulations. Tostran is a clear, colourless gel containing 2% w/w testosterone, which is supplied in a 60 g metered-dose canister and is simple to apply. The metered-dose delivery system of Tostran permits dose adjustment in increments of 10 mg to meet individual patient requirements within the daily dose range of 40–80 mg testosterone. This formulation is indicated for testosterone replacement therapy in male hypogonadism, when testosterone deficiency has been confirmed by clinical symptoms and signs, and laboratory analyses [21].

The gel is applied once daily at approximately the same time each morning and the dose of gel can be adjusted according to

**Table 1** Daily dose ranges for Tostran 2% gel compared with 1% testosterone gels

	Gel daily dose range (g)	Testosterone daily dose range (mg)	Testosterone dose titration unit
Tostran 2% gel	2–4 (4–8 pump activations)	40–80	10 mg metered-dose
Testosterone 1% gel	5–10	50–100	1 or 2 sachets/tubes

clinical or laboratory response, but should not exceed 4 g [21]. With a starting dose of 3 g of gel (60 mg testosterone), 92% of patients are within the normal physiological range of testosterone after only one 20 mg testosterone dose adjustment [22].

Tostran gel is applied to clean, dry, intact skin [21] and the entire dose should be applied to the abdomen (over an area of at least 10 cm by 30 cm) or, alternatively, one-half of the dose may be applied to each inner thigh (over an area of at least 10 cm by 15 cm on each thigh) [21]. The gel is rubbed in gently until the application site is dry, then the application-site is covered, preferably with loose clothing. Application to the abdomen or inner thighs on alternating days is recommended to minimise application-site reactions [21]. Table 1 provides an overview of the daily dosage ranges for Tostran compared with 1% testosterone gels. The lower volume of Tostran used may enhance patient acceptability.

All men receiving testosterone-replacement therapy should be monitored regularly for serum testosterone concentrations, improvements in symptoms and signs, prostate health status (via digital rectal examination and prostate-specific antigen (PSA) testing) and polycythaemia [3].

The main focus of this paper is a clinical trial evaluating the effect of showering on the absorption of testosterone following topical application of Tostran. We also present market research data that support the use of Tostran for testosterone replacement in men with hypogonadism.

### Evaluating the effect of showering on the absorption of testosterone following topical application of Tostran

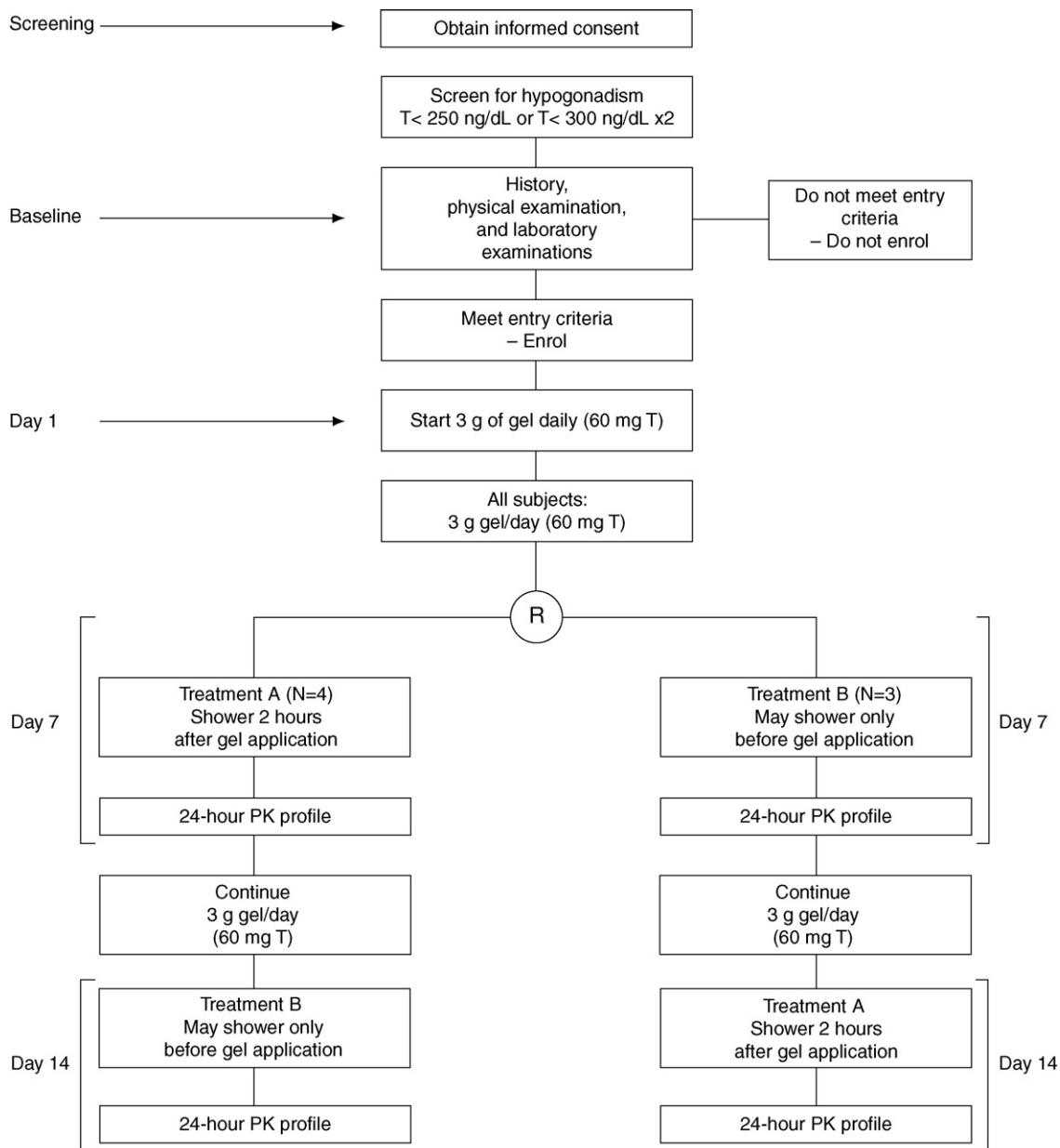
With current 1% testosterone gels, patients are advised not to wash or shower for at least 6 h

after gel application [23,24]. A trial was conducted to evaluate the effect of showering on the absorption of testosterone and resultant serum levels, after topical application of Tostran. This was an open-label, non-vehicle-controlled, randomised, two-treatment, two-period crossover study in seven hypogonadal males aged 18–65 years [ProStrakan Ltd, unpublished results, data on file]. The study protocol was designed to comply with the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice [25] and the Declaration of Helsinki [26].

Hypogonadal male patients who were deemed to be healthy based on medical history, physical examination, electrocardiogram (ECG) and clinical laboratory tests and who did not meet any of the exclusion criteria were enrolled.

For the initial 6 days of treatment, patients applied a single 3 g (60 mg testosterone) dose of Tostran at approximately the same time each morning. On Day 7, patients reported to the study site and were randomly assigned to treatment group AB ( $N = 4$ ) or BA ( $N = 3$ ). Tostran was administered and blood samples were collected over a 24 h period for pharmacokinetic analysis. Patients in the treatment A group had a shower 2 h after the gel had been applied. Patients assigned to treatment B were not permitted to shower during the 24 h period following administration. Following Day 7, patients in both treatment groups continued applying a daily dose of Tostran (60 mg testosterone). On Day 14 all patients were admitted to the study site for a second 24-h serum testosterone profile, in accordance with the cross-over design (Figure 3).

Model-independent methods were used to determine the following serum testosterone parameters for all patients at each treatment phase: area under the concentration versus time curve from time 0 (the time of application) to the end of the dosing interval, approximately 24 h postdose ( $AUC_{0-24}$ ); average

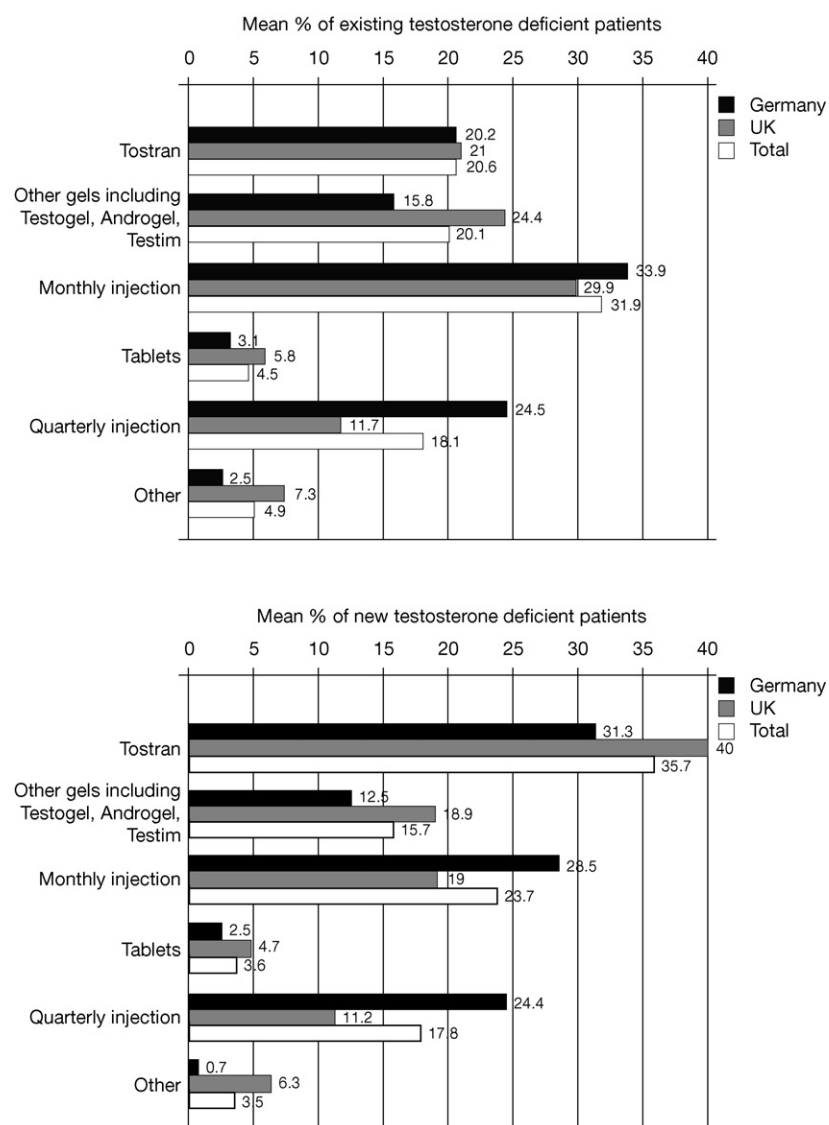


PK, pharmacokinetic; T, testosterone

**Figure 3** Study design of the showering trial for Tostran [ProStrakan Ltd, unpublished results, data on file].

serum concentration ( $C_{avg}$ ); observed maximum serum concentration ( $C_{max}$ ); observed minimum serum concentration ( $C_{min}$ ); time to  $C_{max}$  ( $T_{max}$ ). The  $AUC_{0-24}$  was calculated using the trapezoidal method. All statistical comparisons were performed using analysis of covariance (ANCOVA) and considering the treatment regimen sequence, the treatment phase and regimen, and the patient-within-treatment-sequence. The variation between the mean serum testosterone concentrations

for the two treatment sequences for  $C_{min}$ ,  $C_{max}$ ,  $C_{avg}$  and the corresponding 95% confidence intervals (CI) was calculated on the basis of natural logarithmic transformations. Safety evaluations included: an assessment of treatment-emergent adverse events; an assessment of skin irritation at the application site; screening and exit visit physical examination findings, clinical laboratory results and measurement of vital signs and ECGs.



**Figure 4** Results from questionnaires, completed in the UK and Germany, indicating which formulations endocrinologists would prescribe for existing/new testosterone-deficient patients. The question asked was: 'Assuming Tostran had been available in your country for at least 3 months, what percentage of your existing/new testosterone deficient patients would you treat with each of the following products?' Total number of respondents = 100. Market research conducted by Synovate Healthcare [ProStrakan Ltd, unpublished results, data on file].

## Results

All patients received study medication and none were withdrawn prematurely from the study.

### Tostran absorption is not affected by showering after application

Showering 2 h after application of Tostran had no significant effect on serum testosterone levels; Treatment A,  $AUC_{0-24}$  was 8939 ng-h/dl (standard deviation (SD) = 2107.4); Treatment B,

$AUC_{0-24}$  was 9199 ng-h/dl (SD = 3216.1). The ratio of the geometric means for  $C_{avg}$ ,  $C_{max}$  and  $C_{min}$  were 1.03, 0.83 and 1.29, respectively. These demonstrated that treatments A and B were comparable, without statistical or clinical differences. As a result, patients are advised to wait for at least 2 h only between gel application and bathing or showering [21].

### Safety and tolerability

A single treatment-emergent adverse event was recorded in this study. Haematuria was

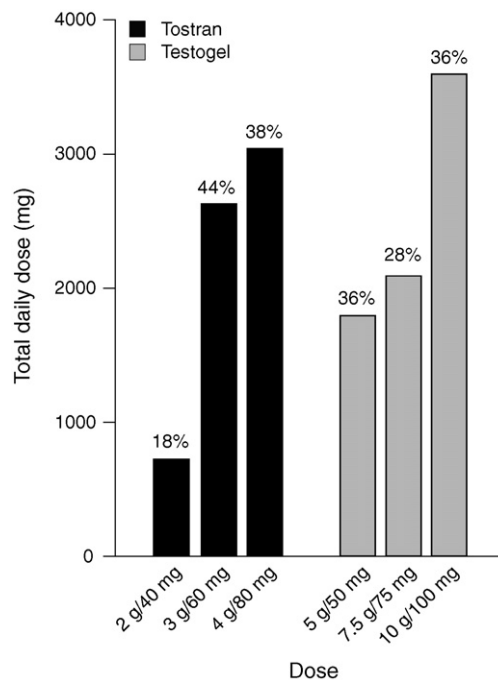
reported by one patient 15 days after the first Tostran dose, 9 days into the second treatment period (Treatment A). This was considered not to be related to the study medication. The event resolved in 5 days without the requirement for further medication. No patient in this trial experienced an application site reaction, a serious adverse event or death. All clinical laboratory test results were within normal limits or were not clinically significant. No clinically significant changes in vital signs or physical examinations were observed between baseline and the final visit to the clinic. In this study Tostran was well tolerated, which is consistent with other testosterone gels.

### Physicians respond positively to the Tostran metered-dose delivery and formulation

With Tostran, serum testosterone levels achieve the normal range from Day 7 onwards [22] and these levels are maintained. Tostran gel is easy to apply, with metered-dose adjustment, compared with other forms of testosterone treat-

ment which require frequent administration (i.e. oral formulation), painful, deep intramuscular injection, or result in wastage if the complete unit dose is not required (i.e. 1% testosterone gels).

Market research conducted in the UK and Germany has indicated that the majority of testosterone-deficient patients in these two countries are currently treated with monthly injections [ProStrakan Ltd, unpublished results, data on file]. When interviewed, 100 endocrinologists said they would consider giving Tostran to 1 in 3 of their new patients and switching 1 in 5 of their treated patients to Tostran (Figure 4) [ProStrakan Ltd, unpublished results, data on file]. The main reasons cited for this preference were the dosage and administration advantages of Tostran together with the ability to shower 2 h post dose. The flexibility of the metered-dose formulation allows for individual dose-titration and could lower the overall cost of therapy when compared with fixed dose tubes and sachets. An average daily testosterone dose of only 64 mg (i.e. 3.2 g of gel) of Tostran is required, whereas an average dose of 75 mg (i.e. 7.5 g of gel) is



**Figure 5** Comparison of testosterone maintenance doses received by patients using Tostran or Testogel/AndroGel<sup>®</sup> in separate dose titration studies [22,27]. Total daily dose was calculated for 100 patients (based on 201 patients for Tostran and 143 patients for Testogel). The average doses taken by all of the patients are 64 mg and 75 mg, respectively (based on 201 patients for Tostran and 143 patients for Testogel).

associated with Testogel/AndroGel<sup>®</sup> (Figure 5) [22,27].

## Conclusion

Short-acting testosterone preparations should be preferred over long-acting depot preparations in men with late onset hypogonadism as the possible development of a contraindication requires rapid discontinuation of treatment [3].

Tostran is a metered-dose 2% testosterone gel formulation that was developed to overcome some of the disadvantages of other available testosterone treatments. Tostran thus has the advantage of an easy to use, metered-dose application that may be adjusted in 10 mg increments by physicians for each individual, while the low volume of gel required in comparison to 1% gels may enhance the acceptability and compliance of patients. This trial demonstrated that showering 2 h after application of Tostran had no significant effect on

serum testosterone levels, giving this medication an advantage over other topically-applied testosterone treatments. The flexibility of the metered-dose formulation allows for individual dose-titration and could lower the overall cost of therapy when compared with fixed dose tubes and sachets. A prospective Phase III trial established that Tostran normalises testosterone levels in >90% of patients, following a single dose adjustment, and is associated with a high rate of compliance [22]. Market research conducted in the UK and Germany indicates that physicians would consider prescribing Tostran in preference to other testosterone products for patients with hypogonadism.

## Acknowledgements

Tostran<sup>®</sup>, Fortigel<sup>®</sup>, Itnogen<sup>®</sup> and Tostrex<sup>®</sup> are registered trademarks of Strakan International Limited. Editorial assistance and publication of the manuscript was supported by the ProStrakan Group.

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