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A new 2% testosterone gel formulation: a comparison with currently available topical preparations

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SUMMARY

Testosterone gel formulations have become a popular testosterone replacement therapy in patients with hypogonadism since their advent in the year 2000. The gel formulations restore testosterone levels to mid-normal physiological levels (14–17.5 nmol/L) as early as within 24 h, and help alleviate the signs and symptoms of testosterone deficiency, thereby leading to an improved quality of life. Although testosterone gels have a favourable efficacy and safety profile as compared to injectable and patch formulations, risk of secondary exposure poses a challenge. Approved testosterone topical formulations include Tostrex® (Tostran®, Fortesta®), Androgel® (Testogel®), Testim® and Axiron® (solution), which have a favourable efficacy profile and positively impacted patient-reported outcome(s). Besides, Testavan, which is a 2% testosterone gel, is under registration in Europe and already approved in Australia in May 2017. Testavan uses a novel hydroalcoholic and highly viscous topical formulation. This product comes with a metered dose dispenser and a cap applicator that allows a hands-free application for precise dispensing and application. The present article provides a comprehensive review of pharmacokinetic, tolerability and safety profile of the testosterone gels available in the market along with the new 2% testosterone gel, Testavan.

INTRODUCTION

The clinical burden of hypogonadism in men has increased notably over the past few years and is associated with a high comorbidity rate, particularly diabetes, metabolic syndrome, cardiovascular diseases and adverse bone health (Kalyani & Dobs, 2007; García-Cruz *et al.*, 2013; Rodriguez-Tolrà *et al.*, 2013; Zarotsky *et al.*, 2014).

Clinically characterized by physiologically low levels of testosterone and symptoms of testosterone deficiency, hypogonadism is reported to have an incidence of 2–6% in men aged 40–79 years (Dohle *et al.*, 2015). Although it primarily affects older population (60–80 years) (Mulligan *et al.*, 2006), hypogonadism is not uncommon in the younger population (Huhtaniemi, 2014). In adolescent and young men, hypogonadism is commonly associated with delayed puberty and absence of/or reduced secondary sexual characteristics (Heaton, 2003). Importantly, in younger men, the prevalence of hypogonadism due to infection with human immunodeficiency virus (HIV) and other systemic diseases is high (Rochira *et al.*, 2011).

Testosterone replacement therapy (TRT) is the most sought after treatment by patients, and the data show that in the US itself, TRT prescription has grown with 359% amidst increasing prevalence of hypogonadism and the increasing awareness of the benefits of TRT in the last decade (Baillargeon *et al.*, 2013). However, a significant proportion of men are receiving TRTs without having their testosterone levels measured, particularly in the primary care setting. In a survey across 41 countries from 2000 to 2011, it was found that off-label prescription of TRT has been increased due to the lack of understanding of the underlying pathophysiology and age-related testosterone deficiency (Handelsman, 2013, 2017). Both national and international guidelines outline the importance of an adequate work-up for correct diagnosis before prescribing TRTs (Lawrence *et al.*, 2017).

There is an array of approved TRTs available, with varying formulations such as injectable products, oral formulations, buccal preparations and topical gels, solutions and patches. The goal of the TRT is to restore testosterone to mid-normal range

(14–17.5 nmol/L), thereby improving the sexual functioning and other symptoms of hypogonadism, and hence an improved quality of life (QoL) (Stanworth & Jones, 2009; Jones *et al.*, 2011; Dohle *et al.*, 2015; Morales *et al.*, 2015). Although most of these preparations are efficacious in achieving the therapeutic levels of testosterone, there are differences in their clinical profile, mode of administration and patient's preference. Some intramuscular preparations, the pioneers in TRT, may lead to pronounced supraphysiological or fluctuating testosterone levels (roller coaster effect), especially the short-acting formulations, and injection itself may cause pain and redness at the injection site (Surampudi *et al.*, 2012; Khera, 2016). However, longer-acting intramuscular preparations of testosterone undecanoate can be adjusted to achieve testosterone levels within the normal range throughout the treatment period. Topical patch preparations, on the other hand, can be associated with skin irritation, while buccal preparations may be associated with unpleasant taste, gum pain and headache (Khera, 2016). Topical testosterone gels, the next-generation formulations, have an edge over these preparations and have gained popularity particularly due to ease of application, good bioavailability, favourable tolerability and reduced occurrence of supraphysiological testosterone levels (Surampudi *et al.*, 2012; Ullah *et al.*, 2014). However, these too have certain safety-related challenges, which need to be addressed and novel formulations be developed.

The present review provides a comprehensive overview of approved testosterone gels, with respect to their pharmacokinetic (PK) profiles, dosing regimens, efficacy, endocrine actions, and safety and tolerability.

METHODS

Literature search and evidence acquisition

To evaluate data on Testavan with historical data of other marketed topical TRTs, a PubMed search was conducted to identify publications from phase II and III studies that evaluated the dose, efficacy, safety and tolerability of marketed topical testosterone gels limited to approved topical TRT in men with hypogonadism. The search terms included, 'testosterone and hypogonadism', 'testosterone replacement therapy', 'testosterone gels and efficacy', 'testosterone gels and safety' and 'testosterone and quality of life'.

DIAGNOSIS AND MANAGEMENT OF TESTOSTERONE DEFICIENCY

Although there are subtle differences in the guidelines evaluating patients with androgen deficiency, most of these recommend the diagnosis to be based on the presence of signs and symptoms along with the serum testosterone (total and free) concentrations.

The symptoms can be categorized as sexual and non-sexual. Sexual symptoms may include erectile dysfunction, reduced morning erections and libido, and difficulty in achieving orgasm. While non-sexual symptoms and signs may include fatigue, endurance and vigour, cognitive decline, depression, anaemia, bone disorders, central obesity and metabolic syndromes (Heaton, 2003; Bhasin *et al.*, 2010; Lunenfeld *et al.*, 2015).

Guidelines indicate that serum total testosterone levels should be routinely measured and be based on morning (usually fasting) serum total testosterone, which is <8 nmol/L or serum testosterone in the range of 8–11 nmol/L, and free testosterone <220 pmol/L (Dohle *et al.*, 2015).

Although serum-free testosterone levels seem to be a reliable measure of testosterone concentration (Livingston *et al.*, 2017), special care should be taken in patients presenting with comorbid conditions like HIV, liver cirrhosis and visceral obesity (Livingston *et al.*, 2017). In such patients, both free and bioavailable testosterone should be evaluated, as the individual variation in SHBG concentrations may influence total testosterone levels (Lunenfeld *et al.*, 2015).

Amidst the variability in diagnostic and therapeutic recommendations, patients and treating physicians are often stuck while making treatment-related decisions. Currently, several preparations of testosterone are available, which may differ in terms of the route of administration or their pharmacokinetics or their adverse events profile. Thus, the selection of a particular TRT should be based on the mutual agreement between the patient and the physician (Dohle *et al.*, 2015).

THE UNMET TREATMENT NEED

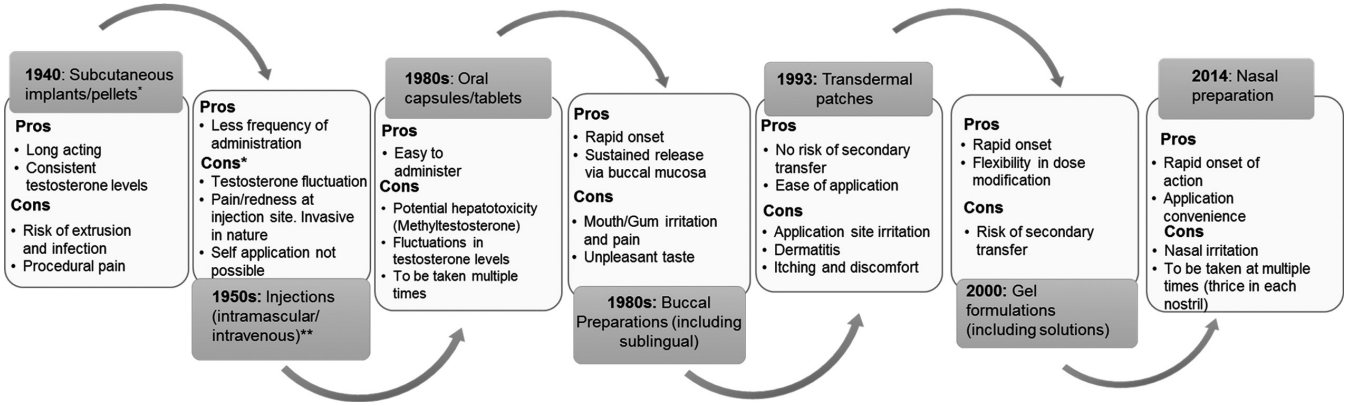
The current portfolio of TRT has shown a positive evolution over the time (Fig. 1). Despite this, there still is an unmet need owing to, for example, poor patient compliance, largely due to inconvenience with administration and secondary safety issues, fluctuations in testosterone levels and tolerability profile (Pfeil & Dobs, 2008).

These challenges majorly compromise the treatment success despite an appropriate diagnosis and effective treatments available and offered. The data show that over 80% of the patients with low total testosterone receive TRT, and however, >85% of these have issues with compliance to TRT, while 36% might not even start or continue the treatment (Gooren, 2016).

The pioneer TRT, that is the intramuscular preparations, had lower dosing frequency but were less patient friendly in terms of invasive nature, and testosterone fluctuations or roller coaster effect. Topical agents, mainly testosterone patches and testosterone gels that emerged soon after, had a better convenience and safety profile. The topical patches, available as scrotal and non-scrotal patches, are not very popular considering the need to shave off the scrotal hairs, and application-related itching, skin irritation and discomfort (Surampudi *et al.,* 2012). Topical testosterone gels are available as hydroalcoholic topical formulations containing 1–2% of testosterone and currently stand as the most preferable TRT.

Even though the advent of testosterone gel formulations has remodelled the TRT and treatment regimen, the benefit-risk aspects need to be carefully evaluated and addressed. The gel preparations have optimum efficacy in achieving and maintaining the serum testosterone levels within physiological range, low potential for skin irritability, and can be customized based on the treatment response. However, gels are associated with an increased risk of secondary exposure and may lead to virilization in women and premature puberty in children (Surampudi *et al.,* 2012). This calls for a gel with an improved novel formulation that not only enhances the absorption but also achieves and maintains serum testosterone levels within physiological range, allows for a safer application and conceptualizes a treatment regimen that can be optimised based on the treatment response.

Figure 1 Evolution of testosterone replacement therapies with time. *In a major advancement in the treatment of hypogonadism, Nebido (Aveed), a long-acting depot testosterone undeconoate, was developed, which came to UK market in the year 2005. This formulation was designed to achieve levels of testosterone within the normal healthy range and is most commonly used in Europe after gel preparations. **Approved in the USFDA in the year 1982.



DEVELOPMENT OF TOPICAL TESTOSTERONE FORMULATIONS

Androgel® 1% was the first topical gel formulation developed. The starting dose is 5 g (50 mg testosterone), which could be applied by hand over the shoulders/both arms/ abdomen. As a line extension, it was also approved in the EU as Androgel® 1.62%, with a starting dose of 2.50 g (40.5 mg of testosterone), dispensed by two pump actuations and applied by hand over both shoulders and upper arms (Swerdloff *et al.*, 2000; Kaufman *et al.*, 2011, 2012). Testim® (Testosterone 1%) was the second gel developed as a unit dose of 5 g tube of 1% strength containing 50 mg of testosterone, applied to the shoulders by hand (Steidle *et al.*, 2003). Another product, Tostrex® (Tostran®), was developed as a 2% gel with a starting dose of 3 g (60 mg of testosterone, dose could range from 20 to 80 mg, 20 mg increments), which could be applied to the abdomen or inside of both thighs by hand using a pump dispenser (*SmPC Tostran*). Similar to Tostrex®, Fortesta® 2% is applied to inner thighs with a starting dose of 40 mg testosterone, adjusted in 10 mg testosterone increments for dose flexibility, with a minimum dose of 10 mg and a maximum dose of 70 mg testosterone (Dobs *et al.*, 2012).

Axiron® is a 2% testosterone solution, approved in the United States and in some EU countries as well, with a starting dose of 60 mg. It is delivered via a metered pump that delivers 3 mL (30 mg) of testosterone to each underarm with single actuation (Khera, 2016).

Testavan, the new 2% testosterone gel, uses a novel hydroalcoholic and highly viscous topical formulation. The product is homogeneous, transparent and non-staining, and comes in a metered dose dispenser that includes a hands-free cap applicator for precise dispensing and application. The starting dose is 23 mg testosterone, delivered by one pump actuation, contained in 1.15 g of gel, and the highest dose is 3.45 g of gel containing 69 mg testosterone (delivered by three pump actuations) (Efros *et al.*, 2016).

Compared to the other topical products, the amount of gel used with Testavan is generally less than the other products due to its higher bioavailability owing to its composition. In a randomized, active-controlled phase I study in down-regulated men, Testavan showed higher testosterone bioavailability, while delivering more testosterone in a small volume as compared with Androgel® (Olsson *et al.*, 2014). Also, there is no intended secondary exposure to the hands, which minimizes the risk of secondary exposure.

DATA FROM THE CLINICAL STUDIES

The published data for topical testosterone gels delve around efficacy, ease of gel application, dose titration regimens, PK, effect of showering on the absorption of the gel from the site of application and safety, particularly risk of interpersonal gel transfer and supraphysiological levels of serum testosterone. All these factors together seem to govern the choice of both the user and the prescribing physician.

The efficacy of a TRT depends upon its ability to bring the average serum testosterone levels (C_{ave}) to a normal physiological range. Guidelines suggest that TRT should restore the serum testosterone level to the mid-normal physiological range, which is usually sufficient to alleviate various manifestations of testosterone deficiency, apart from improving the QoL (Dohle *et al.*, 2015; Morales *et al.*, 2015). Also, it is important to know what proportion of patients (responders) had their serum testosterone levels normalized following treatment as it will indicate the proportion of patients that will be benefitted from the treatment in clinical practice. Furthermore, it should be noted that the benefit in terms of resolution of signs and symptoms, patient's satisfaction with the treatment is one of the important efficacy and compliance indicators, and should be weighed accordingly.

Serum testosterone concentration

Consistent with the guidelines, in two multicentre phase III studies, the mean C_{ave} levels achieved with Testavan ranged from 12.8 to 17.5 nmol/L, similar to those achieved with Androgel® 1.62%, Tostrex® 2%, Fortesta® 2% Testim® 1% and Axiron® solution (Table 1). Figure 2 shows the testosterone levels over time for C_{ave} responders at Day 90 (*Unpublished data*).

Testavan gel provides the option of lowest starting dose of 23 mg testosterone, which could go up to 46, and 69 mg as the maximum dose. The advantage of lower starting dose with Testavan comes from **F**erring **A**dvanced **S**kin **T**echnology (FAST), a proprietary topical gel technology developed by Ferring Pharmaceuticals. FAST relies on a unique combination of volatile/non-volatile solvents and permeation enhancers that temporarily increase the skin permeability and hence reduces the volume of

Table 1 Mean C_{ave} for various testosterone products

Testosterone gel	Sampling Day	Dose level of testosterone	Mean C_{ave} (nmol/L)	*N*
Testavan (Cunningham *et al.*, 2017)	90	23 mg/day	12.8 ± 4.2	5
		46 mg/day	17.5 ± 7.2	45
		69 mg/day	15.2 ± 5.7	89
Androgel® 1% (Swerdloff *et al.*, 2000)[a]	180	50 mg/day	19.2 ± 1.2	51
		50 to 75 mg/day	450 ± 3.7	20
		100 to 75 mg/day	744 ± 2.6	20
		100 mg/day	713 ± 1.0	52
Fortesta® 2% (Dobs *et al.*, 2012)	90	All levels, 10 to 70 mg/day	15.2 ± 5.7	100
Testim® 1% (Steidle *et al.*, 2003)	90	50 mg/day	13.8 ± 8.1	99
		100 mg/day	17.1 ± 8.2	106
Axiron® 2% (Wang *et al.*, 2011)	120	30 mg/day	17.11 ± 8.29	3
		60 mg/day	17.56 ± 6.07	97
		90 mg/day	14.40 ± 5.73	25
		120 mg/day	13.53 ± 5.55	10

C_{ave}, average concentration. [a]Values for Androgel® 1.62% not available.

applied gel without high residual volume. However, as with most of the topical agents, risk of secondary exposure, especially for women and children, and the washout of testosterone while rinsing hands or showering is expected with Testavan also and has been thoroughly evaluated.

Dose titrations and fluctuations

Although less frequent, topical gel/solution formulations could be associated with fluctuations outside the physiological range, even with the recommended dosing and titration regimen. Such fluctuations could be attributed to variations in skin blood flow owing to skin temperature, perspiration or other local environmental factors (Gooren & Bunck, 2003). However, it should be noted that most of the approved topical TRT products are administered daily and show a peak (T_{max}) at 2–4 after application and gradually decline until next day, which mirrors the normal testosterone diurnal variation (Swerdloff *et al.*, 2000) (Kaufman *et al.*, 2011).

As fluctuations outside the physiological range might precipitate unwanted signs and symptoms, it is important to evaluate both the testosterone levels following treatment and reduction in hypogonadal signs and symptoms. Often, the supra-physiological fluctuations with topical TRTs in peak testosterone levels (i.e. C_{max}) outside the eugonadal range are short, isolated and sporadic, which infrequently affect testosterone/dihydrotestosterone ratios (T/DHT) (Swerdloff *et al.*, 2000; Steidle *et al.*, 2003; Wang *et al.*, 2011). Generally, these fluctuations are noted while optimising the dose, and the ability of the titration regimen to consistently preclude or minimize exposure to supra-physiological testosterone excursions (Kaufman *et al.*, 2011; Cunningham *et al.*, 2017). In other instances, such isolated peak fluctuations are often explainable by sample errors, sample site contamination, and are not considered to be associated with unfavourable side effects.

The subphysiological testosterone levels during the initiation and dose adjustment phase are another concern and need to be evaluated and addressed. Assessment of pharmacodynamic endpoints (luteinizing hormone suppression, haemoglobin increase) together with serum testosterone levels adds valuable information, and might resolve fluctuations following dose optimisation. Furthermore, testosterone levels may fall below 10.4 nmol/L in normal men for few hours during the day (Kelsey *et al.*, 2014), which could also happen during the treatment with any of the TRT including the topical gel preparations.

To further understand the impact of testosterone fluctuations, it is worthwhile to see the effect on T/DHT ratio. The available data for testosterone gels show that T/DHT ratio is steadier with topical TRT products compared to, for example, intramuscular TRT (Gooren, 2016). Therefore, the risk of adverse effects associated with testosterone fluctuations outside the normal range occurring with the topical TRTs is considered to be minimal. Nevertheless, to ensure patient safety, guidelines suggest a cautious dose monitoring in patients with pre-existing cardiovascular disease and care should be taken so that the testosterone levels do not exceed the mid-normal physiological range (FDA advisory committee report; Advisory Commitee Industry Briefing Document, 2017). This calls for a greater focus on the optimised dosing regimens and dose titrations.

In-line with this, a meticulous dose titration scheme was designed for Testavan in the pivotal study (study 000127). The focus was also on maintaining the normal physiological range for testosterone and DHT and reduces the instances of supraphysiological testosterone levels (Cunningham *et al.*, 2017).

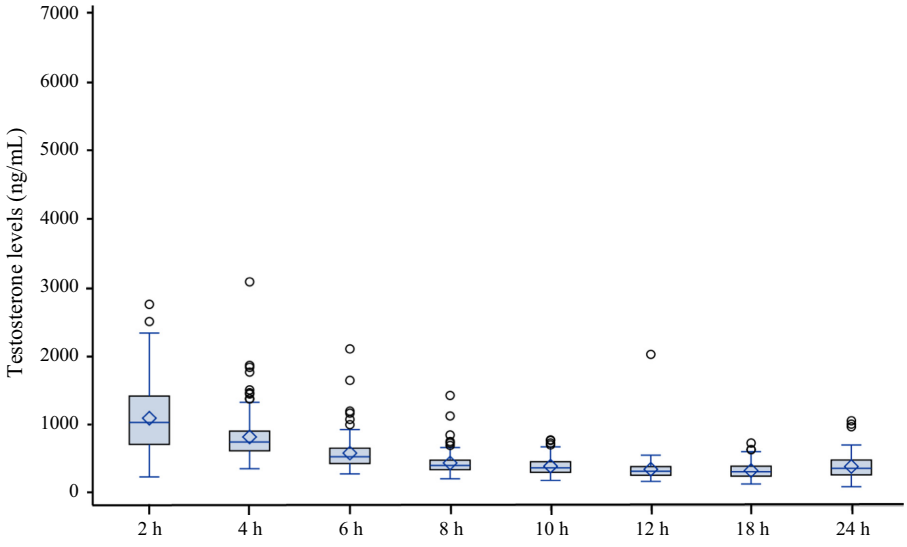


Figure 2 Box plots of total testosterone level over time for C_{ave} responders at Day 90, Phase 3 trial with Testavan. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 2 Posology of various testosterone gels

	Testavan (Cunningham *et al.*, 2017)	Androgel® 1% (Swerdloff *et al.*, 2000)	Androgel® 1.62% (Dean *et al.*, 2004)	Tostrex® 2% (*SmPC Tostran*)[a]	Fortesta® 2% (Dobs *et al.*, 2012)[a]	Axiron® 2% (Wang *et al.*, 2011)
Starting dose	23 mg/day (one actuation)	50 mg/day (one sachet)	40.5 mg (two actuations)	60 mg (3 g of gel)	40 mg (2 g of gel, 4 pump actuation)	60 mg (30 mg on each axilla)
Application method	Cap applicator	By hand	By hand	By hand	By hand	Cup applicator
Dosage	23–69 mg/day	50–100 mg/day	20.25–81 mg/day	10–80 mg/day	10–70 mg/day	60–120 mg/day
Doses available	3 doses; 23 mg, 46 mg, 69 mg	3 doses; 50 mg, 75 mg, 100 mg	4 doses; 20.25 mg, 40.5 mg, 60.75 mg, 81 mg	5 doses; 10 mg, 20 mg, 40 mg, 60 mg, 80 mg	7 doses; 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	4 doses; 30 mg, 60 mg, 90 mg, 120 mg
Application site	Shoulders and/or upper arms	Shoulders and/or upper arms	Shoulders and/or upper arms	Abdomen or to both inner thighs	Front and inner thighs	Both axilla
Recommended dose titration	4 h post-dosing on Day 14, 35 and 56 after treatment initiation	Pre-dosing, in morning before application, 3–7 days after treatment initiation	Pre-dosing, in morning before application, Day 14 and Day 28 after treatment initiation	2 h post-dosing, Day 14 after treatment initiation	2 h post-dosing, on Day 14, 35 and 60 (±3) days after treatment initiation	2 h post-dosing, on Day 45, based on the Day 15 average testosterone concentration

[a]Tostrex 2% and Fortesta 2% are the same products with different start dose and dosing regimens. While Tostrex/Tostran 2% is approved in EU, Fortesta 2% is approved in the USA.

A dose as low as 23 mg was selected as the starting dose in pivotal study of Testavan. The initial dose was either maintained or up-titrated to either 46 or 69 mg testosterone based on 4-h post-dose serum testosterone concentrations. Similarly for Tostrex®, the serum testosterone levels for dose titration are measured 4 h post-dose, although its starting dose is 60 mg (Table 2). A lower starting dose enables steadier rise of testosterone to eugonadal levels and minimises the episodes of supraphysiological testosterone levels in hypogonadal men. It should also be noted that this increases the titration by two steps, considering that 69 mg dose could be the appropriate dose for a particular patient.

On the other hand, the starting dose of 50 mg for Testim® and Androgel® 1% and 60 mg for Tostrex® and Axiron® is at a higher end than with the starting doses for Testavan, suggesting a good bioavailability of Testavan. For Axiron®, the dose could be down-titrated to 30 mg if C_{avg} on day 15 was 36.4 nmol/L or could be up-titrated to 90 mg if C_{avg} was 10.4 nmol/L. (Table 2). Moreover, both Testim® and Androgel® (both 1% and 1.62%) involve sample collection for measuring serum testosterone prior to the application of gel (Table 2). This is plausibly problematic as the peak testosterone levels reached only after dose administration and dose titration prior to gel administration will not be suggestive of the post-dose testosterone levels.

An important aspect of dosing with topical gels is also to ensure that the correct volume of gel, and hence, testosterone is applied. Testavan comes with a metered dose pump provided with a cap applicator that minimises the margin of error in dose titrations and ensures that a precise amount of dose is delivered to the application site rather than getting transferred to patient's hand. The pump delivers precisely 23 mg of testosterone gel with each actuation.

Responder rate

Responder rate with the TRTs forms the base of their approval. As per regulatory requirements, the responder rate has to be at least 75% for any testosterone gel to be approved; that is, at least 75% of the treated men should achieve normal physiological levels of serum testosterone (C_{ave}, 10.4 to 36.4 nmol/L). The responder rates for Fortesta® and Tostrex® in two separate studies were 77.5% (Dobs *et al.*, 2012) and 84.1% (FDA PK assessment report, Tostrex), respectively. For Axiron® and Androgel®, the responder rates were 84.1% (Wang *et al.*, 2011) and 82.1% (Kaufman *et al.*, 2011), respectively. For Testavan, the responder was >75% in the pivotal study (Cunningham *et al.*, 2017), and >82% (Belkoff *et al.*, 2017) in two supportive studies. The responder rates at multiple time points for various testosterone gels are presented in Table 3.

Effect of showering on absorption

To ensure an adequate absorption of testosterone from the topically applied gel, it is recommended to have a gap of 2 h between gel application and engaging in activities like showering and swimming as these activities might washout the drug prior to adequate absorption. However, at times, there could be a non-compliance with this recommendation. Therefore, it is important to determine the impact of showering on drug absorption at different time points, and this aspect has been studied in detail.

For Androgel® 1%, showering 15 or 30 min after gel application resulted in >50% reduction in testosterone absorption. The mean average testosterone levels reduced from 994 ± 1026 to 34.5 ± 8.6 nmol/L and 13.9 ± 8 nmol/L following showering after 15 and 30 min, respectively. It is thus recommended that showering should be avoided for at least 5 or 6 h after gel application (de Ronde *et al.*, 2011). For Androgel® 1.62%, showering resulted in 14% and 10% in area under curve for 24 h. (AUC_{0-24}) at 2 and 6 h, respectively (Stahlman *et al.*, 2012a,b). It was concluded that washing the site of gel application 2 h after gel application does not impact the bioavailability; on the contrary, it reduces the residual testosterone on the skin, and hence, chances of secondary transfer are reduced. For Tostrex®, showering after 2 h only was evaluated, and it did not have any significant effect on the PK of testosterone. Therefore, the product label recommends

Table 3 Responder rates (percentage of patients with testosterone within eugonadal range)

	Testavan gel[a] (Cunningham *et al.*, 2017)	**Testavan gel**[a] (Belkoff *et al.*, 2017)		**Androgel**®[b] **1.62%** (Kaufman *et al.*, 2011)	**Tostrex**®[c] **2%** (*FDA PK assessment report, Tostrex*®)	**Fortesta**®[c] **2%** (Dobs *et al.*, 2012)	**Axiron**®[d] **2%** (Wang *et al.*, 2011)
		000023	000077 (6-month extension study)				
Number of patients allocated to TRT	160	180	145	234	201	149	155
				Percentage responder (CI)			
Day 90, EOT	76.10 (69.4, 82.8)	85.5 (80.2, 90.7)	–	–	–	77.5 (70.3, 84.7)	–
Day 112/120	–	–	–	81.60 (75.1, 87.0)	–	–	84.10 (78, 90.2)
Day 182, EOT	–	–	82.1 (74.3, 89.3)	82.20 (75.6, 87.7)	95.2 (91.7, 98.7)	–	–

EOT, end of trial; TRT, testosterone replacement therapy; confidence interval (CI) presented wherever available. [a]Responder rate defined as percentage responders with total testosterone Cave values within 10.4 to 36.4 nmol/L. [b]Responder rate defined as percentage responders with total testosterone Cave values within 10.4 to 34.7 nmol/L. [c]Responder rate defined as percentage responders with total testosterone Cave values within 10.4 to 39.5 nmol/L. [d]Responder rate defined as percentage responders with total testosterone Cave values within 10.4 to 36.4 nmol/L.

waiting at least 2 h between application and showering (FDA PK assessment report, Tostrex). For Axiron®, a decrease of 35% of testosterone exposure was observed on washing the application site at 2- and 6-h post-testosterone application (*Company data sheet, Axiron*). Patients are thus advised to avoid swimming or washing the application site until 2 h following application of Axiron®.

For Testavan, showering at 1 and 2 h after gel application decreased the C_{ave} by 19.2% and 14.3%, respectively, compared to no showering. On the other hand, showering 6 h following administration of Testavan did not result in a decrease in C_{ave} (*unpublished data*). Overall, the effects of showering on the absorption of testosterone from Testavan were similar to the effects reported for other testosterone gel products approved in the EU and the United States. These findings suggest that a gap of at least 2 h between application of gel and bathing will not have significant impact on the testosterone levels, particularly washing off the site of gel application.

Patient-reported outcomes (PROs)

PRO_s form an integral part of efficacy assessment of an intervention, especially when disease takes a toll on the physical and psychological status. Men with hypogonadism often present with fatigue, reduced energy and low sexual drive that severely affects their QoL.

TRT in patients with hypogonadism leads to a significant improvement in multiple signs and symptoms of testosterone deficiency, viz. fatigue, sexual functioning, bone health, muscle mass and psychological health, and QoL (Table 4).

Treatment with Testavan caused a significant improvement in International Index of Erectile Function (IIEF) and Multidimensional Assessment of Fatigue (MAF) scores, and Short Form 12 (SF-12) Health Survey total scores following a three-month treatment period in phase II and III studies. The benefit was sustained for a continued treatment for up to six months (Efros *et al.*, 2016; Belkoff *et al.*, 2017; Cunningham *et al.*, 2017). This is comparable with that reported with Androgel® (Pexman-Fieth *et al.*, 2014; Snyder *et al.*, 2016), Axiron® (Burns *et al.*, 2015), Testim® (Steidle *et al.*, 2003) and Tostrex® (Jones *et al.*, 2011)

SAFETY CONSIDERATIONS

Some patients with a poor general health status (malnourished, obese or chronic illnesses) may develop hypogonadism as a consequence of such conditions, and restoration to normal serum testosterone might be associated with increased risk of side effects, including major adverse cardiovascular events (Corona *et al.*, 2014; Decaroli & Rochira, 2017).

Overall, testosterone gels are the most investigated and preferred TRT formulations for the treatment of male hypogonadism wherein a significant amount of literature supports the safety profile of testosterone gels (Layton *et al.*, 2015; McBride *et al.*, 2015). The most common adverse drug reactions reported in <8% of patients include acne, headache, emotional liability, nervousness, abnormal dreams and gynaecomastia (Table 5a,b). A potential safety consideration is the risk of secondary exposure, especially in women and children. This also impacts the choice of both the user and the prescribing physician and has a direct impact on the patient compliance.

Risk of secondary exposure

Owing to their topical application, testosterone gels increase the risk of inadvertent interpersonal transfer and secondary exposure causing virilization in women and premature puberty in children. Although the risk of secondary exposure might reduce if physical contact is made after showering, this has not been studied separately for any of the approved gels (Stahlman *et al.*, 2012a,b). Following reports of secondary exposure with both Testim® and Androgel®, the FDA mandated the inclusion of black box warning regarding the potential skin-to-skin-transfer in their label. Early clinical studies with Testosterone 2% gel showed that there was no apparent secondary exposure in non-treated women following contact with treated male partner provided the application site was covered with a cloth or a contact was made after male partner had taken a shower (*unpublished data*).

As it is difficult to control the lifestyle-related factors impacting the secondary exposure leading to virilization of exposed females and precocious puberty in children, developing formulations that are quickly absorbed using minimal application volume, and allow the use of cap applicators are highly warranted. Testavan was developed on similar lines, which uses an improved formulation that utilizes a novel permeation-enhancing system. This minimizes the application volume necessary for restoration of normal testosterone levels and provides higher bioavailability and a fast absorption, minimizing residual active drug. This formulation can be applied using a

Table 4 Testosterone gels and patient-reported outcomes

Study design	*N*	Treatment	Efficacy end-point(s)	Result	Outcome conclusion
Testavan (Cunningham *et al.*, 2017) Open-label, non-comparator	159	Testosterone gel (FE 999303) 2%: 23, 46 or 69 mg daily based on titration criteria for 3 months	Changes from baseline in IIEF parameters	Erectile function domain: 5.9 ± 8.1 Intercourse satisfaction domain: 2.4 ± 3.6 Orgasmic function domain: 1.8 ± 3.5 Sexual desire domain: 2.2 ± 2.1 The overall satisfaction domain: 2.1 ± 2.5 $p < 0.0001$ for all parameters	Significant improvement in sexual functioning
			Changes from baseline in MAF parameters	Severity: −5.2 ± 4.9 Distress: −2.2 ± 2.5 DIADD: −16.7 ± 16.7 Timing: −3.0 ± 3.4 $p < 0.0001$ for all parameters	Significant improvement in fatigue parameters
			Changes from baseline in SF-12 health survey	PCS score: −1.8± 7.1 $p < 0.05$ MCS score: −6.5 ± 10.1 $p < 0.000$	Significant improvement in QoL
Androgel® Open-label, observational study (Pexman-Fieth *et al.*, 2014)	1049	Testosterone gel 1%: 50, 75 or 100 mg of for 6 months	Change from baseline in AMS scale	Responders: −14.7 ± 12.0 Non-responders: −12.1 ± 11.9 ($p < 0.05$)	Significant improvement on ageing symptoms
			Change from baseline in IIEF	Responders: 18.2 ± 18.5 Non-responders: 16.9 ± 16.8	Improvement in erectile functioning
			Change from baseline in MFI	Responders: −16.8 ± 19.2 Non-responders: −10.7 ± 22.3 $p < 0.005$	Significant improvement in general, physical, and mental state with enhanced activity and motivation
Coordinated set of seven double-blind, placebo-controlled (Snyder *et al.*, 2016)	790 adult hypogonadal males (n =394 in each group) Note: Patients could participate in more than one study	Testosterone gel 1% for 12 months	**Sexual function study**		Significant improvement in sexual activities, erectile function and sexual desire
			Change from baseline in the PDQ-Q4 score	PDQ-Q4 score: 0.58 (0.38 to 0.78), $p < 0.001$	
			Change from baseline in the erectile function domain score of IIEF	IIEF erectile function score: 2.64 (1.68 to 3.61), $p < 0.001$	
			Change from baseline in the sexual-desire domain score of DISF-M-II	DISF-M-II sexual desire score: 2.93 (2.13 to 3.74), $p < 0.001$	
			Physical function study		Significant improvement in physical function (walking capacity) after treatment
			Change from baseline in the PF-10 score	PF-10 score: 3.06 (1.18 to 4.94), $p < 0.005$	
			Vitality Study		Significant improvement in vitality (energy), affect, and depression with no significant improvement in fatigue after treatment
			Change from Baseline in the FACIT-Fatigue scale score	FACIT-fatigue score: 1.21 (−0.04 to 2.46)	
			Change from Baseline in the SF-36 – vitality score	SF-36 vitality score: 2.41 (0.31 to 4.50), $p < 0.05$	
			Change from Baseline in the PANAs-positive and negative affect score	PANAS-positive affect score: 0.47 (0.02 to 0.92), $p < 0.05$ PANAS negative affect score: −0.49 (−0.79 to −0.19), $p < 0.001$	
			Change from Baseline in the PHQ-9 depression scale score	PHQ-9 depression score: −0.72 (−1.20 to −0.23), $p < 0.005$	

(continued)

Table 4 (continued)

Study design	*N*	Treatment	Efficacy end-point(s)	Result	Outcome conclusion
Double-blind,randomized, placebo-controlled	40	Testosterone gel: 50 mg for 3 months	Change from baseline in the IIEF score (15-item score and 5 functional domain score)	IIEF: 14.4 ± 15.9 $p < 0.005$ vs. baseline and placebo	Significant improvement in erectile functioning with sexual desire and orgasmic satisfaction insignificantly affected
Tostrex® (Jones *et al.*, 2011)					
Double-blind, randomized, placebo-Controlled	220 adult hypogonadal men with type-2 diabetes (n =108 in testosterone group and n =112 in placebo group)	Testosterone gel 2% for 12 months	Change from Baseline in IIEF score	IIEF score: 40.9 ±20.34 p <0.05	Significant improvement in sexual function
Axiron® (Burns *et al.*, 2015)					
Phase IV, open-label, single-arm study years with diagnoses of hypogonadism, with total testosterone <10.4 nmol/L when they were treated with the highest dose of a topical testosterone gel tolerated by the patient	78 men ≥18 years	Testosterone solution 2% for 9 months	**PGI–severity**	**Energy level**	**Sexual drive** Treatment with Axiron led to improvement in energy level in 75% of patients (58/78) and sexual drive improved in 70% (54/78)
			Normal, not at all ill	30 (38.46)	29 (37.18)
			Mildly ill	20 (25.64)	10 (12.82)
			Moderately ill	25 (32.05)	21 (26.92)
			Severely ill	3 (3.85)	18 (23.08)
			PGI–Improvement	**Energy level**	**Sexual drive**
			Very much better	8 (10.39)	6 (7.79)
			Much better	23 (29.87)	21 (27.27)
			A little better	27 (35.06)	27 (35.06)
			No change	17 (22.08)	22 (28.57)
			A little worse	2 (2.60)	1 (1.30)
			Much worse	0 (0.00)	0 (0.00)
			Very much worse	0 (0.00)	0 (0.00)

AMS, aging males' symptoms; DISF-M-II, derogatis interview for sexual functioning in men-II; FACIT, functional assessment of chronic illness therapy; IIEF, international index of erectile function; MAF, multidimensional assessment of fatigue; MCS, mental component summary; MFI, multidimensional fatigue inventory; PANAs, positive and negative affect schedule; PDQ-Q4; PGI: patient global impression; psycho-sexual daily questionnaire; PCS, physical component summary; PF-10, physical function domain scores; PHQ-9, patient health questionnaire 9; QOL, quality of life; SF-12, short form 12 health survey; SF-36, short-form health survey; TRT, testosterone replacement therapy.

metered dose dispenser and a cap applicator, which limits/eliminates the use of hands, thereby lowering the risk of secondary exposure. This was evident in the phase III study wherein all patients were either satisfied or very satisfied with the cap applicator, with 87% of patients feeling that using the cap applicator reduced the risk of secondary exposure (Cunningham *et al.*, 2017). This dispensing mode is not available for any of the approved testosterone gel formulation. Axiron® solution is the only topical formulation that utilizes an applicator for applying testosterone to the axillae, and minimizes the risk of secondary exposure. However, there is not much available data that may support the ease and convenience of using this applicator (Wang *et al.*, 2011).

Application site tolerability

Some gel formulations have demonstrated an edge over other topical formulations, which are frequently associated with erythema and irritation (Lakshman & Basaria, 2009). Having said this, the problem could be reduced to a considerable extent if the patients switch the application site daily.

The data from phase III study of Androgel® 1.62% and its extension study show that 0.9% and 1.6% patients with adverse events (AEs), respectively, discontinued due to application site AEs (Kaufman *et al.*, 2012). A relative high proportion of patients experienced AEs with Tostrex® 2% (16.8% patients; 1.3% withdrawals due to an AE) (FDA PK assessment report, Tostrex) and Testim® 1% (5.9% patients; 1.1% withdrawals due to an AE) (Dean *et al.*, 2004). Similarly for Axiron®, skin reactions (17%) were the most commonly reported AEs and included skin irritation (7%) and erythema (8%) with one patient discontinuing due to application site reaction (Muram *et al.*, 2012). In another study with Axiron®, applications site reactions (12%) have been reported as the most common AEs (Wang *et al.*, 2011).

Testavan has shown a good application site tolerability with few occurrences of pruritus (1.1%), rash (1.7%) and skin irritation (1.1%) in one of its phase III study (Study 000023) (Belkoff *et al.*, 2017). Furthermore, application site reactions observed were as low as 4.4% in the pivotal study (000127), with only two patients withdrawing from the study (Cunningham *et al.*, 2017). These data provide an indirect evidence and support the safety of the novel formulation Testavan.

ADVERSE EVENTS OF SPECIAL INTEREST

Cardiovascular events

The association between TRT and cardiovascular risk is still unclear. However, evidence suggests that normalization of testosterone may reduce cardiovascular events and mortality (Baillargeon *et al.*, 2013; Muraleedharan *et al.*, 2013). Having said this, more prospective data need to be collected to deduce a scientific consensus.

Prostate safety

Although two extension studies with Androgel® 1.62% (3-year study) and Testim® 1% (1-year study) reported sporadic incidences of prostate cancer (<1%, three cases each for both studies), the evidence remains poor as none of the studies were adequately

Table 5 (a) Incidence of adverse events (≥1%); open-label studies. (b) Incidence of adverse events (≥1%); placebo-controlled studies

Preferred term AEs≥1%	**Testavan** (Cunningham *et al.*, 2017; *NCT02149264*)	**Testavan** (Belkoff *et al.*, 2017; *NCT01665599*; *NCT01703741*)		**Androgel® 1.62%** (Kaufman *et al.*, 2012)	**Tostrex® 2%** (*FDA PK assessment report, Tostrex*)*	**Fortesta® 2%**** (Kaufman *et al.*, 2012)	**Axiron® 2%** (Wang *et al.*, 2011)	**Axiron® 2%** (Brock *et al.*, 2016a)
		000023	000077					
(a)								
Total number of patients included	160	180	145	191	201	149	155	558
Number of patients analysed for safety	159	180	145	191	201	149	155	558
Number of patients with at least one AE	54 (33.96%)	62 (34.4%)	28 (19.3%)	79 (41.4%)	160 (79.6%)	69 (46.3%)	81 (52.3%)	262 (46.9%)
Withdrawal due to AEs	7	1	2	17	32	5	-	29
AEs of special interest								
Application site reactions	7 (4.4%)	-	-	-	109 (54.2%)	25 (16.8%)	19 (12.2%)	-
Increased PSA	2 (1.26%)	3 (1.7%)	-	10 (5.2%)	4 (2.0%)	-	2 (1%)	-
Prostatitis	-	-	-	2 (1%)	-	-	-	-
Benign prostatic hyperplasia	-	-	-	2 (1%)	-	-	-	-
Increased HCT	-	-	4 (2.8%)	2 (1%)	-	-	6 (3.9%)	28 (5.02%)
Increased haemoglobin	-	2 (1.1%)	2 (1.4%)	-	-	-	-	-
Other frequent AEs								
Bronchitis	5 (3.1%)	-	-	2 (1%)	-		-	-
Upper respiratory tract infection	5 (3.1%)	6 (3.3%)	-	10 (5.2%)	-	10 (6.7%)	-	19 (3.4%)
Nasopharyngitis	4 (2.5%)	2 (1.1)	-	5 (2.6%)	-	-	6 (3.9%)	19 (3.4%)
Cough	5 (3.1%)	-	-	-	-	-	-	-
Pyrexia	2 (1.26%)	-	-	-	-	-	-	-
Increase in blood triglyceride	3 (1.9%)	4 (2.2%)	-	2 (1%)	-	-	-	-
Fatigue	-	-	-	2 (1%)	-	-	-	-
Gastroenteritis viral	-	-	-	2 (1%)	-	-	-	-
Viral infection	2 (1.3%)	-	-	-	-	-	-	-
Joint sprain	2 (1.3%)	-	-	-	-	-	-	-
Nausea/Vomiting	2 (1.3%)	-	-	-	-	-	4 (2.6%)	-
Blood glucose increased	2 (1.3%)	-	-	-	-	-	-	-
Gamma-glutamyl transferase increased	2 (1.3%)	2 (1.1%)	-	-	-	-	-	-
Hypertriglyceridaemia/ Hyperlipemia	2 (1.3%)	-	-	2 (1%)	4 (2.0%)	-	-	-
Decreased libido	-	-	-	2 (1%)	-	-	-	-
Pneumonia	-	-	-	2 (1%)	-	-	-	-
Pollakiuria	-	-	-	2 (1%)	-	-	-	-
Tendon rupture	-	-	-	2 (1%)	-	-	-	-
Back pain	2 (1.3%)	-	-	2 (1%)	-	-	-	-
Headache	-	2 (1.1%)	-	2 (1%)	-	-	8 (5.2%)	-
Herpes zoster	-	-	-	2 (1%)	-	-	-	-
Hypertonic bladder	-	-	2 (1.4%)	-	-	-	-	-
Pruritus	-	2 (1.1%)	-	-	-	-	-	-
Insomnia	2 (1.3%)	-	-	2 (1%)	-	-	-	-
Pharyngolaryngeal pain	-	-	-	2 (1%)	-	-	-	-
Epididymitis	2 (1.3%)	-	-	-	-	-	-	-
Erectile dysfunction	2 (1.3%)	-	-	-	-	-	-	-
Hypertension	2 (1.26%)	3 (1.7%)	2 (1.4%)	4 (2.1%)	10 (5.0%)	-	-	-
Diarrhoea	-	-	-	2 (1%)	-	-	4 (2.6%)	-
Influenza	-	-	-	3 (1.6%)	-	-	-	-
Sinusitis	-	-	-	3 (1.6%)	-	6 (4%)	-	-
Acne	-	-	-	3 (1.6%)	-	-	-	-
Arthralgia	-	-	-	2 (1%)	-	-	-	6 (1.08%)
Ear+labyrinth disorders	-	-	-	-	-	-	-	6 (1.08%)

Preferred term AEs≥1%	**Androgel®** (Kaufman *et al.*, 2011)		**Axiron®** (Brock *et al.*, 2016b)		**Androgel®** (Snyder *et al.*, 2016)	
	Androgel 1.62%	Placebo	Axiron 2%	Placebo	Androgel 1%	Placebo
(b)						
Number of patients	274		715		790	
Number of patients analysed for safety	234	40	354	356	394	394
Number of patients with at least one AE	130 (55.6%)	15 (37.5%)	149 (42.1%)	144 (40.5%)	Information not available	Information not available
Withdrawal due to AEs	25	-	8	11	-	-
AEs of special interest						
Increased PSA	23 (9.8%)	-	6 (1.8%)	3 (0.93%)	23 (5.84%)	8 (2.03%)
Increased HCT	-	-	9 (2.5%) HCT increased > 54%: 6 (1.8%)	2 (0.56%) HCT increased >54%: 1 (0.29%)	-	-
Prostate cancer/neoplasm	-	-	-	1 (0.28%)	1 (0.25%)	-
IPSS>19	-	-	-	-	27 (6.85%)	26 (6.60%)
Haemoglobin ≥17.5 g/dL	-	-	-	-	7 (1.78%)	-
Dermatitis contact	5 (2.1%)	-	-	-	-	-
Application site rash	-	-	4 (1.1%)	10 (2.8%)	-	-
Skin irritation	-	-	4 (1.1%)	9 (2.5%)	-	-
Other frequent AEs						
Cardiac disorders	-	-	-	1 (0.28%)	-	-
Angina unstable requiring hospitalization	-	-	-	1 (0.28%)	-	-

(continued)

Table 5 (continued)

Preferred term AEs≥1%	**Androgel®** (Kaufman *et al.*, 2011)		**Axiron®** (Brock *et al.*, 2016b)		**Androgel®** (Snyder *et al.*, 2016)	
	Androgel 1.62%	Placebo	Axiron 2%	Placebo	Androgel 1%	Placebo
Nervous system disorders	-	-	-	1 (0.28%)	-	
Myocardial infarction, stroke or death from cardiovascular causes	-	-	-	-	7 (1.78%)	7 (1.78%)
Myocardial Infarction (definite/probable)	-	-	-	-	2 (0.51%)	1 (0.25%)
Stroke (definite/probable)	-	-	-	1 (0.28%)	5 (1.27%)	5 (1.27%)
Upper respiratory tract infection	11 (4.7%)	-	8 (2.3%)	6 (1.7%)	-	-
Nasopharyngitis	5 (2.1%)	-	8 (2.3%)	11 (3.1%)	-	-
Decreased HDL	-	-	14 (4.4%)	8 (2.5%)	-	-
Back pain	7 (3%)	-	-	-	-	-
Headache	7 (3%)	2 (5.0%)	3 (0.85%)	8 (2.3%)	-	-
Insomnia	7 (3%)	1 (2.5%)	-	-	-	-
Hypertension	6 (2.6%)	-	-	-	-	-
Diarrhoea	5 (2.1%)	-	-	-	-	-
Myalgia	5 (2.1%)	-	-	-	-	-
Arthralgia	-	-	8 (2.3%)	4 (1.1%)	-	-
Ear infection	-	-	-	6 (1.7%)	-	-
Pulmonary embolism	-	-	-	1 (0.28%)	-	-
Venous thrombosis limb	-	-	-	1 (0.28%)	-	-

AE, adverse event; HCT, haematocrit; HDL, high-density lipoprotein; IPSS, international prostate symptom score; PSA, prostate-specific antigen; TRT, testosterone replacement therapy. *Data taken from FDA PK assessment report (study T 00-02-01); body as a whole (63 {31.3%}) and respiratory system (40 {19.9%}) were also reported as AEs in study T 00-02-01. **AEs≥4%.

powered to detect the incidence of prostate cancer (Dean *et al.*, 2004; Kaufman *et al.*, 2012). Moreover, a retrospective analysis on 47 men suggested that administration of testosterone gels was not associated with the significant increase in the prostate-specific antigen (PSA), irrespective of whether the men had history of prostate cancer or not (Pastuszak *et al.*, 2015).

In-line with the previous data, Testavan showed that of 339 patients, only seven patients had PSA >0.1 nmol/L with a mean change from baseline of 0.24 ± 0.67 ng/dL (Belkoff *et al.*, 2017; Cunningham *et al.*, 2017). In the pivotal study of Testavan, four patients with confirmed PSA levels >0.1 nmol/L at various time points during the study, were found to having PSA levels <0.1 nmol/L upon retesting during rest of the study period (Cunningham *et al.*, 2017). Overall, treatment with testosterone gel has shown good safety profile with respect to prostate cancer as shown in a 5-year follow-up of three registries (Haider *et al.*, 2015), and other previous studies (Raynaud *et al.*, 2013; Eisenberg *et al.*, 2015).

Erythropoiesis and haematocrit events

Topical formulations are linked with a dose-dependent increase in the erythropoiesis. This is due to the fact that testosterone dose dependently stimulates erythropoiesis by increasing erythropoietin levels and suppresses hepcidin levels. Therefore, the guidelines recommend periodic monitoring and dose adjustment if haematocrit is >54% (Bhasin *et al.*, 2010), and one or more dose titrations (or venesection) might be considered in these patients if the reduction in testosterone dose leads to a resurgence of symptoms.

In a one year study with Androgel® 1.62%, four patients discontinued due to haematocrit levels >54%, although it was not clear that either dose adjustment or venesection was done for those patients (Kaufman *et al.*, 2012). Treatment with Testim® 1% gel was frequently associated with altered haematology parameters; 4.9% of the patients had an increase in haematocrit levels, and one patient discontinued the treatment due to elevated haematocrit (Dean *et al.*, 2004). In these cases, one should exclude sleep apnoea and if present, refer these subjects to treatment.

Similarly, increased haematocrit was reported in all phase III studies of Testavan, although the frequency was low. Of 339 patients, only five had haematocrit >54%, 1.2% patients reported an event of increased haematocrit, and two withdrew from the study due to elevated haematocrit levels (Belkoff *et al.*, 2017; Cunningham *et al.*, 2017).

CONCLUSION

It is apparent that there is an unmet need to have testosterone gels with good local tolerability, facilitated by quick absorption with a user-friendly application method that not only delivers precise dose but also limits the risk of secondary exposure. Newer products with a novel composition like Ferring's Testavan have an efficacy and safety comparable to the currently approved gels, while addressing the currently unmet needs. Dispensing Testavan using a metered dose dispenser with a cap applicator, elicited a normal physiological response for serum testosterone levels while improving the fatigue, sexual functioning and QoL, with an acceptable safety and better tolerability profile comparable to that of approved testosterone. Additionally, its proprietary technology enhances the skin permeability, requiring lesser quantity of the gel and thus less active drug on the skin. This further minimises the risk of secondary transfer and provides a similar efficacy with the lowest available dose. Furthermore, the 4-h post-dose titration schema ensures that an optimised dose is administered (23, 46 mg or 69 mg) based on the patient's serum testosterone levels while minimising the risk of reaching supraphysiological testosterone levels. Testavan provides a novel and improved alternative when compared to approved TRT agents based on these criteria, and is therefore a promising TRT agent. A limitation of this review was the unavailability of the comparator-controlled trials, and thus, the data do not come from studies that directly compare different testosterone gels with each other. Most of the trials conducted with the testosterone gels and discussed hereby were either open-label or placebo-controlled. However, as testosterone is a laboratory-based end-point, a comparison between studies is considered feasible.

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DISCLOSURES

Nothing to disclose.

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