7.6 Testosterone

8098F Testosterone Subcutaneous implant 100mg Merck Sharp & Dohme (Australia) Pty Ltd
8099G Testosterone Subcutaneous implant 200mg Merck Sharp & Dohme (Australia) Pty Ltd
8460G Testosterone Transdermal patches 12.2 mg (releasing approximately 2.5 mg per 24 hours), *Androderm*®, Hospira Pty Ltd
8619P Testosterone Transdermal patches 24.3 mg (releasing approximately 5 mg per 24 hours), *Androderm*®, Hospira Pty Ltd
8830R Testosterone Transdermal gel 50mg in 5 g sachet, *Testogel*®, Bayer Australia Ltd
2114G Testosterone enanthate, Injection 250mg in 1mL, *Primoteston Depot*®, Bayer Australia Ltd
2115H Testosterone undecanoate, Capsule 40mg, *Andriol Testocaps*®, Merck Sharp & Dohme (Australia) Pty Ltd
9004X Testosterone undecanoate, I.M injection 1,000mg in 4mL, *Reandron 1000*®, Bayer Australia Ltd

The following product is now deleted from the PBS as of January 2012, but is included for analysis as it was listed for the duration of this review:

2101N Testosterone esters, Injection 250mg, *Sustanon*®, Merck Sharp & Dohme (Australia) Pty Ltd

Purpose
This review examines the utilisation of PBS listed testosterone including analysis by age, gender and prescriber speciality according to prescription count; Defined Daily Dose per 1000 population and government expenditure.

Summary of the main points of the review for the Committee

- Utilisation of testosterone has doubled over the past 5 years.
- Expenditure has increased more than the growth in utilisation. This suggests that therapeutic relativities may require review.
- The listing of two products, testosterone gel and intramuscular injection 1000mg, have driven the growth in the market.
- There is a trend towards more GPs initiating therapy.
- There may be some use of testosterone that is not within the PBS restriction.
- There are some safety concerns with testosterone including possible increased cardiovascular risk in older men.

All PBS listed testosterone products currently have the same restriction:

Authority required:
Androgen deficiency in males with established pituitary or testicular disorders;

Androgen deficiency in males 40 years and older who do not have established pituitary or testicular disorders other than aging, confirmed by at least two morning blood samples taken on different mornings;

Androgen deficiency is confirmed by testosterone less than 8 nmol/L, or 8-15 nmol/L with high LH (greater than 1.5 times the upper limit of the eugonadal reference range for young men);

Micropenis, pubertal induction, or constitutional delay of growth or puberty, in males under 18 years of age.

Background

A recent article in the Medical Journal of Australia[1] stated that progressive increase in PBS-subsidised testosterone prescribing, without changes in proven medical indication or improvements in diagnosis of pathologically based androgen deficiency, is likely to be due to promotion driven, non-compliance with PBS criteria. At the June 2012 meeting DUSC noted the concern raised in the article and considered a review of these agents timely.

Previous DUSC reviews

Prior reviews conducted by DUSC for testosterone have been undertaken in 2003 and 2004. The DUSC review in 2003 found that usage of testosterone capsules remained stable after the listing of the patches, and that the listing of patches resulted in an increased net cost to the PBS. DUSC considered that use of the patches had stabilised following initial rapid uptake and may have indicated unmet need.

The 2004 review found that the listing of the higher strength of the patch strength reduced the use of the lower strength, but the total usage of both patches increased, as did the overall market of testosterone products on the PBS. The review also noted use in a small number of females. DUSC considered that there may be some errors in data collection through the use of a generic Medicare patient number. Some of these patients may also be transgender patients.

PBS listing history

The various formulations of testosterone for the stated indication have been listed at staggered intervals on the PBS, with the drug in clinical use since the 1930's. The current products, route and frequency of administration, date of listing and basis for listing are summarised in the table below.

Table 7.6.1: Drug formulation, dosing and listing details.

Drug name and formulation	Max Qty	Max Rpt	Dose and frequency of administration	Date of PBS listing	Basis for listing
Testosterone Subcutaneous implant 100mg	6	0	600mg -800mg every 4-6 months	Nov 1996	
Testosterone Subcutaneous implant 200mg	3	0	600mg -800mg every 4-6 months	Nov 1996	
Testosterone transdermal patch 12.2 mg (releasing 2.5 mg per 24 hours) *Androderm*®	1 (60 ptch)	5	Apply 1 patch (5mg/24hr) each night. Adjust dose using (2.5mg/24hr) usual range 2.5-7.5mg daily.	Nov 2000	Cost-min with testosterone undecanoate capsules. 2 patches 12.2 mg daily equi-effective to six 40mg caps
Transdermal patches 24.3 mg (releasing approximately 5 mg per 24 hours) *Androderm*®	1 (30 patches)	5	Apply 1 patch (5mg/24hr) each night. Adjust dose using (2.5mg/24hr) usual range 2.5-7.5mg daily.	Nov 2002	Minor submission
Testosterone Transdermal gel 50mg in 5 g sachet *Testogel*®	1 (30 sachets)	5	Apply 5g (equiv 50mg) once daily. Adjust in 2.5g (half a sachet) to max 10mg daily.	Aug 2005	Cost-min to patches, equi-effective doses being the gel 50 mg per day and patch releasing 5 mg day.
Testosterone enanthate I.M injection 250mg in 1mL *Primoteston Depot*®	3	3	250mg every 2-3 wks	Pre-1974	
Testosterone undecanoate Capsule 40mg *Andriol Testocaps*®	60	5	120-160 mg daily for 2-3 weeks then adjust to 80-120 mg daily	Apr 1990	
Testosterone undecanoate I.M injection 1,000mg in 4mL *Reandron 1000*®	1	1	1g every 10-14 weeks	Aug 2006	Cost minimisation with implants. The equi-effective doses were 1g every 10-14 weeks and implant (600 mg) every 4-5 months.*
Testosterone esters I.M Injection 100 mg and 250mg *Sustanon*®			250 mg every 2-3 weeks 100 mg was deleted in 2011.	Pre- 1966	

Frequency of administration taken from AMH 2012, for indication of male hypogonadism, use in delayed puberty requires approximately half the dose.

When recommending the listing of testosterone undecanoate 1000mg I.M. injection (Reandron®) in November 2005, on a cost-minimisation basis as compared to testosterone implant with a dose relativity of testosterone intramuscular injection 1000 mg every 10 - 14 weeks and testosterone implant (600 mg) every 4 months, the PBAC noted that the cost minimisation is reliant on an average three monthly rate of administration of the injection and requested that the Drug Utilisation Sub-Committee (DUSC) monitor the use of the injection following PBS listing. In the event that PBS usage becomes more frequent, the PBAC may wish to revisit the dose relativities.

At the March 2012 meeting, the PBAC recommended the Authority Required listing of testosterone solution for topical administration (Axiron®, Eli Lilly Pty Ltd) on a cost minimisation basis compared with testosterone gel, following its deferral at the November 2011 PBAC meeting pending TGA approval. The equi-effective doses are considered to be testosterone solution 70 mg and testosterone gel 50 mg.

The PBAC expressed concerns about the potential use of testosterone products in populations in whom the drug has not been evaluated as being cost effective.

Results

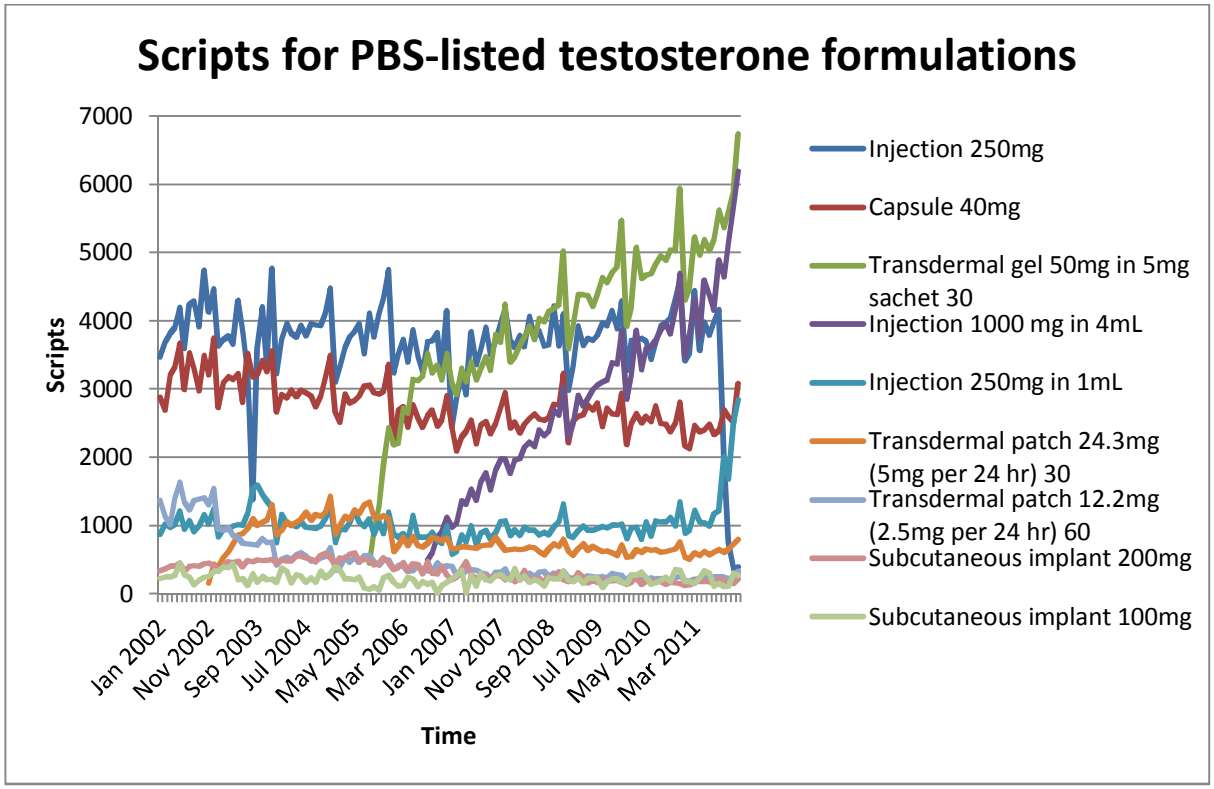


Figure 7.6.1. Number of prescriptions for testosterone (including under-copay and private)
Source: *DUSC database accessed July 2012*

The number of prescriptions has increased dramatically, doubling in the past 5 years. Most of the growth can be attributed to the more recently listed products ie 1000mg intramuscular injection and transdermal gel.

The transdermal gel has had the greatest market share according to the number of prescriptions since it was listed in August 2005. In the most recent month, a similar number of prescriptions for 1000mg I.M. injections have been supplied. However prescription numbers are not directly comparable as one prescription of gel provides 30 days of treatment, whereas one I.M. injection provides 10-14 weeks of treatment.

Following deletion of testosterone esters 250mg injection (Sustanon®) from the PBS, there has been increased use of testosterone enanthate 250 mg injection (Primoteston depot®).

Figure 7.6.2 presents utilisation by DDD/1000 population/day.

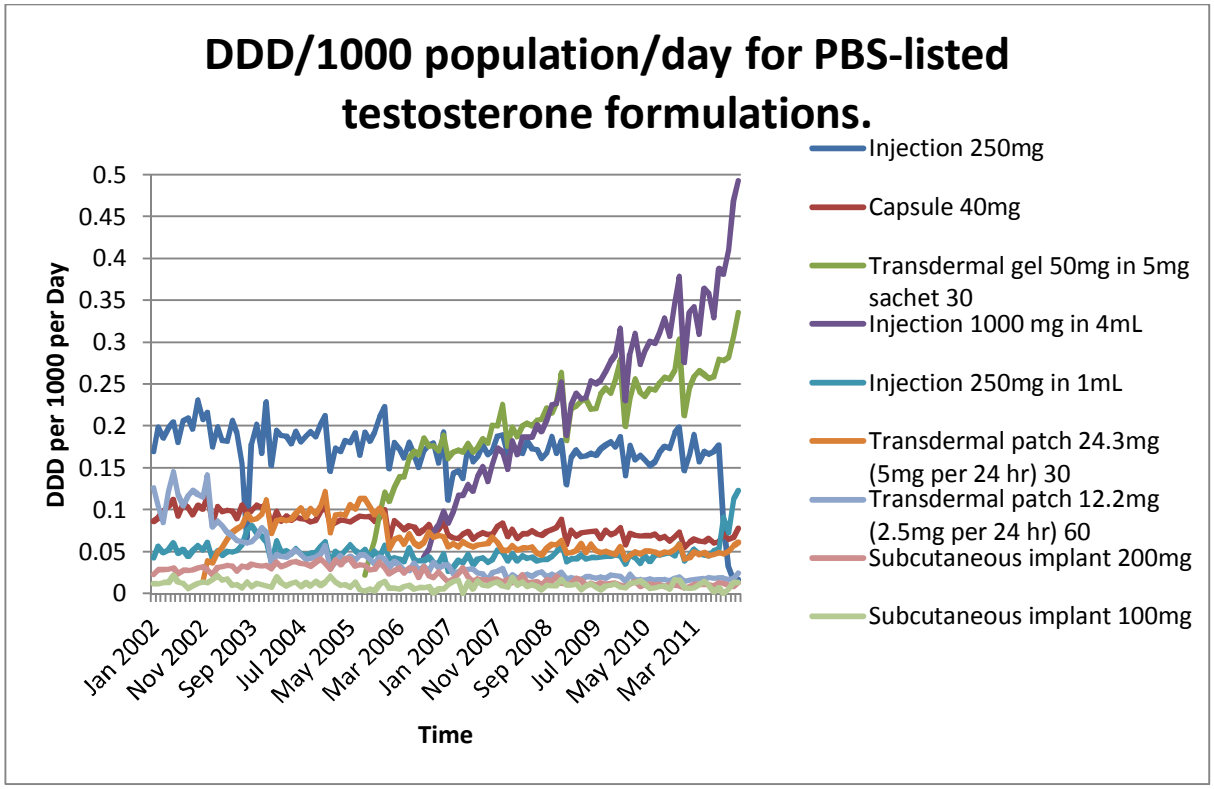


Figure 7.6.2. DDD/1000 population/day for all PBS listed testosterone preparations. Source: *DUSC database accessed August 2012. Data includes R/PBS and private prescriptions.*

The WHO DDDs are based on use in substitution therapy in male hypogonadism. The DDDs for patches are given in amount of testosterone delivered. Individual DDD values are included in the appendix to this report.

The analysis by DDDs/1000population/day confirms that there has been significant and constant growth in the use of testosterone from mid-2005 onwards

In this analysis, testosterone undecanoate IM injection (given every 10-14 weeks) is the market leader, followed by testosterone transdermal gel. Both of these products, listed on a cost-minimisation basis to existing products, resulted in growth of the total market following listing on the PBS.

Figure 7.6.3 show R/PBS expenditure.

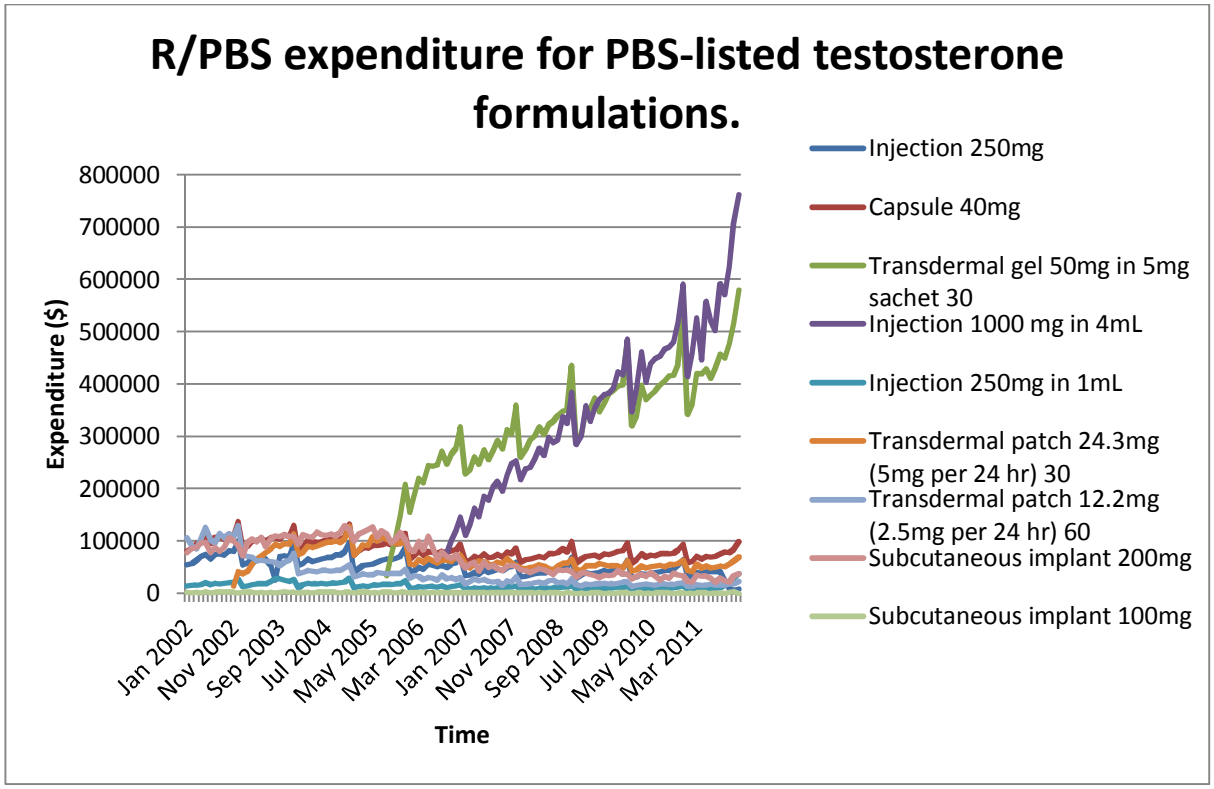


Figure 7.6.3. R/PBS expenditure for all PBS listed testosterone preparations.
Source: *DUSC database accessed August 2012.*

In 2011, government expenditure for testosterone preparations was $14.6 million, up from $5.6 million in 2005. An overall growth of 260%.

The following table compares the rate of growth, year on year, for prescription volume, DDD/1000population/day and expenditure.

Table 7.6.1 Growth rates

Year of supply		2005	2006	2007	2008	2009	2010	2011
Scripts		3.73%	8.09%	9.48%	11.28%	6.45%	5.71%	1.86%
DDDper1000perday		2.86%	12.01%	15.58%	13.68%	7.42%	7.11%	5.42%
R/PBS expenditure ($)		4.44%	29.29%	20.48%	17.59%	14.47%	11.00%	11.72%

Source: summarised data from Figures 7.6.1-3.

It can be seen that growth is not proportional across the various measures of utilisation. The difference in scripts and DDD/100pop/day is due to relative differences in the quantity of testosterone provided in one script. This changes over time as the market share for products alters. The relatively higher growth in expenditure suggests that the principles of cost-minimisation may not be realised and dose relativities may need to be reconsidered.

To better understand factors driving the growth further analyses were conducted:

Prescriber type for initiation scripts

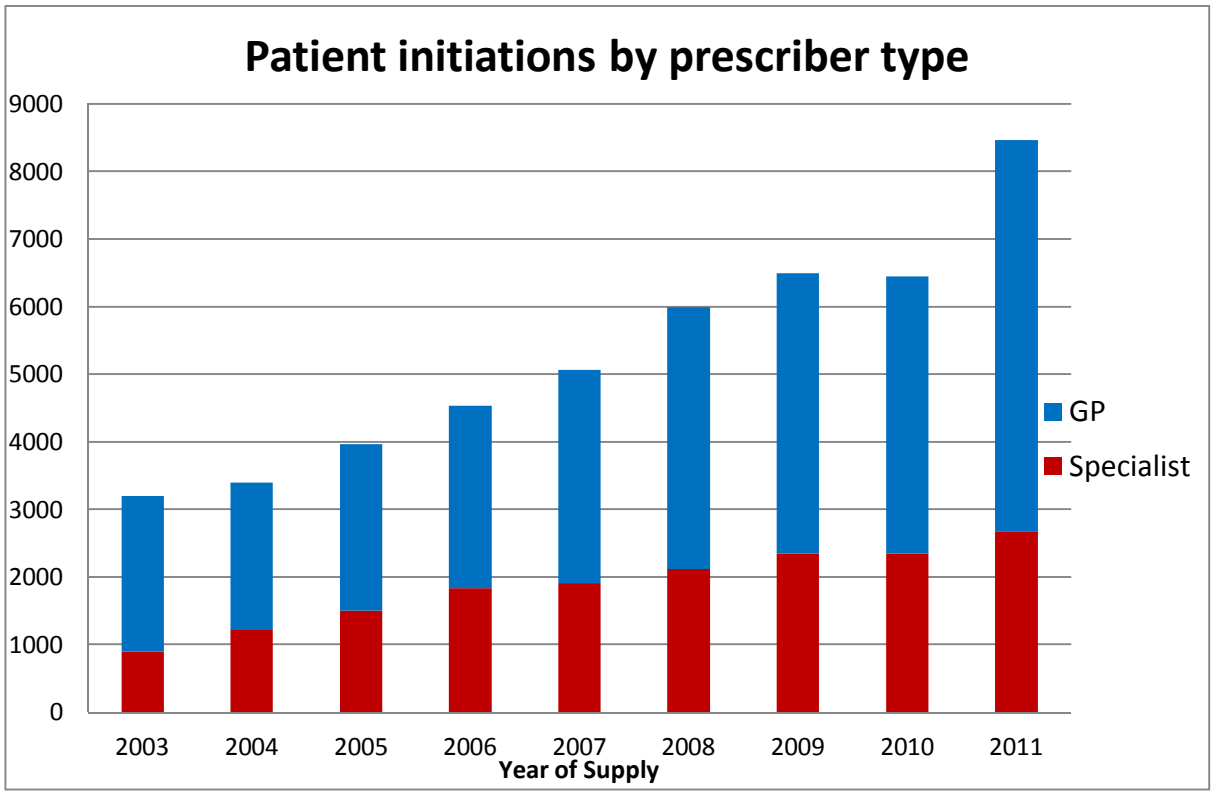


Figure 7.6.4 Initiations of testosterone by prescriber type. Initiation is defined as no script for testosterone in at least the prior 12 months.
Source: Medicare DHS, PBS Supplied Script database, extracted August 2012.

The proportion of initiations by GPs has increased over time. In the most recent year almost all of the growth has been driven by GP prescribing.

R/PBS and private market comparison

To assess if there has been any shift in the proportion of use via PBS and private prescriptions the following analysis was conducted:

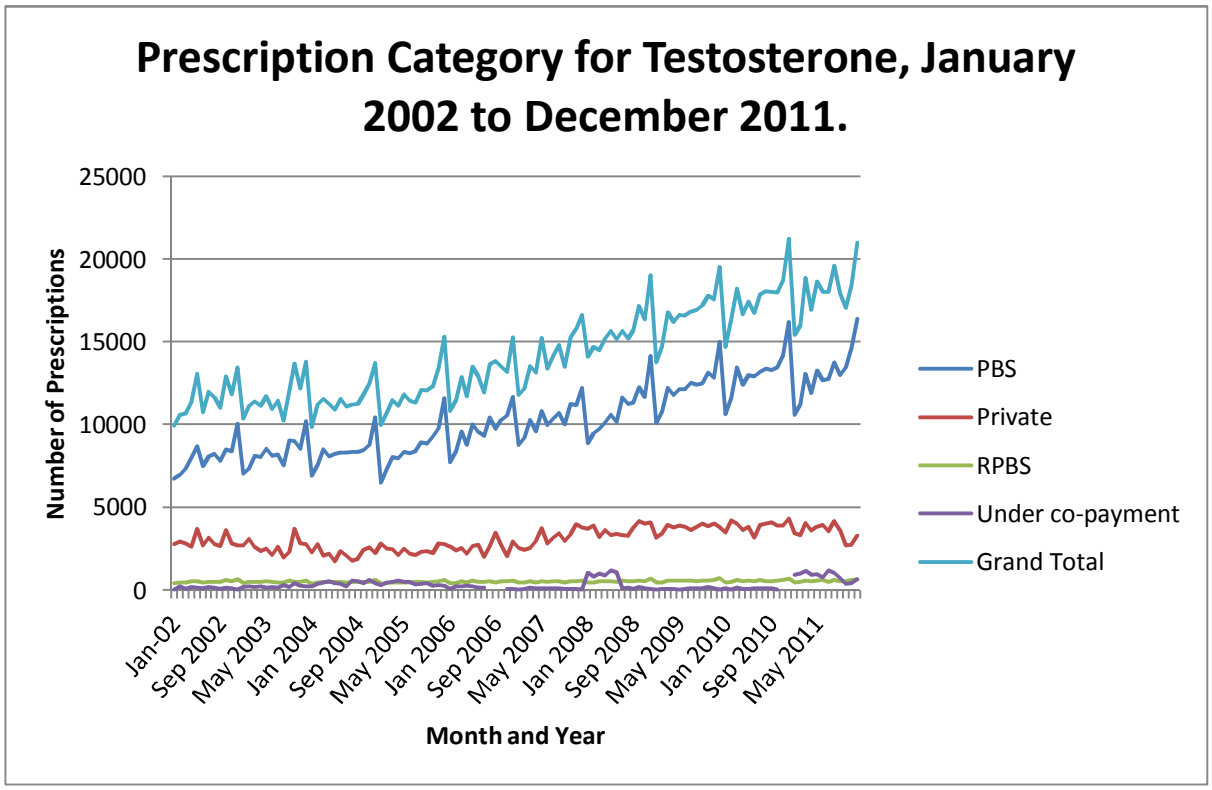


Figure 7.6.5 Number of prescriptions by category
Source: DUSC database, accessed July 2012.

Private prescribing has remained stable. Almost all growth in the testosterone market can be attributed to R/PBS supply.

Age of patients at initiation:

Figures 7.6.6 and 7.6.7 examine the age of patients initiating on therapy in terms of the absolute patients numbers and as a proportion of total patients over time, respectively.

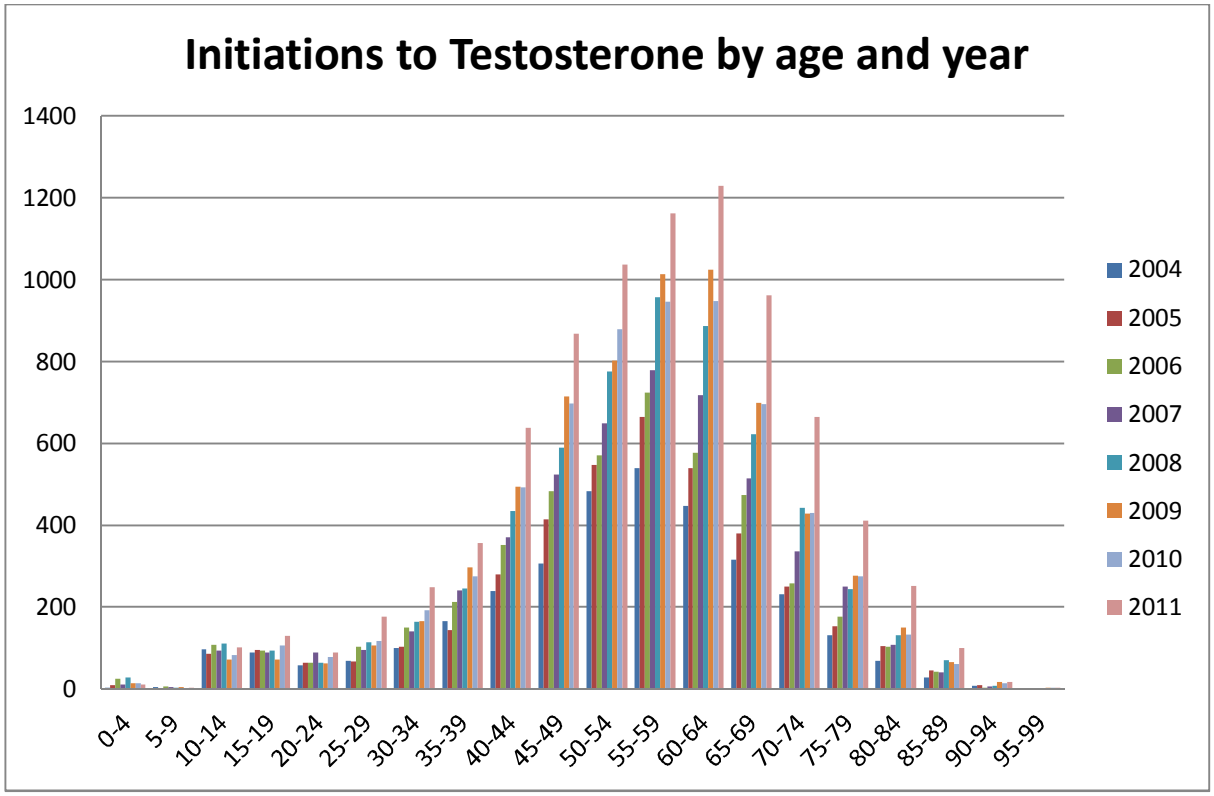


Figure 7.6.6 Number of patients by age initiating testosterone therapy each year.
Source: *Medicare DHS, PBS Supplied Script database, extracted August 2012.*

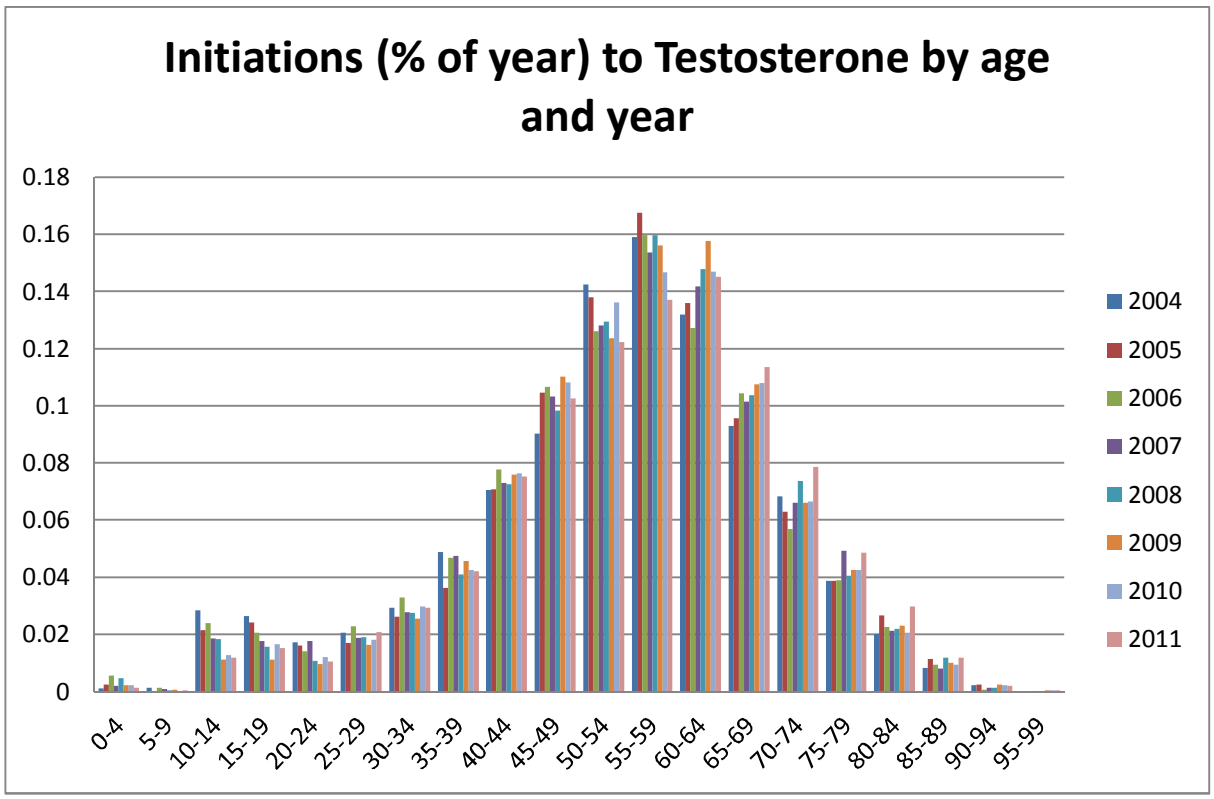
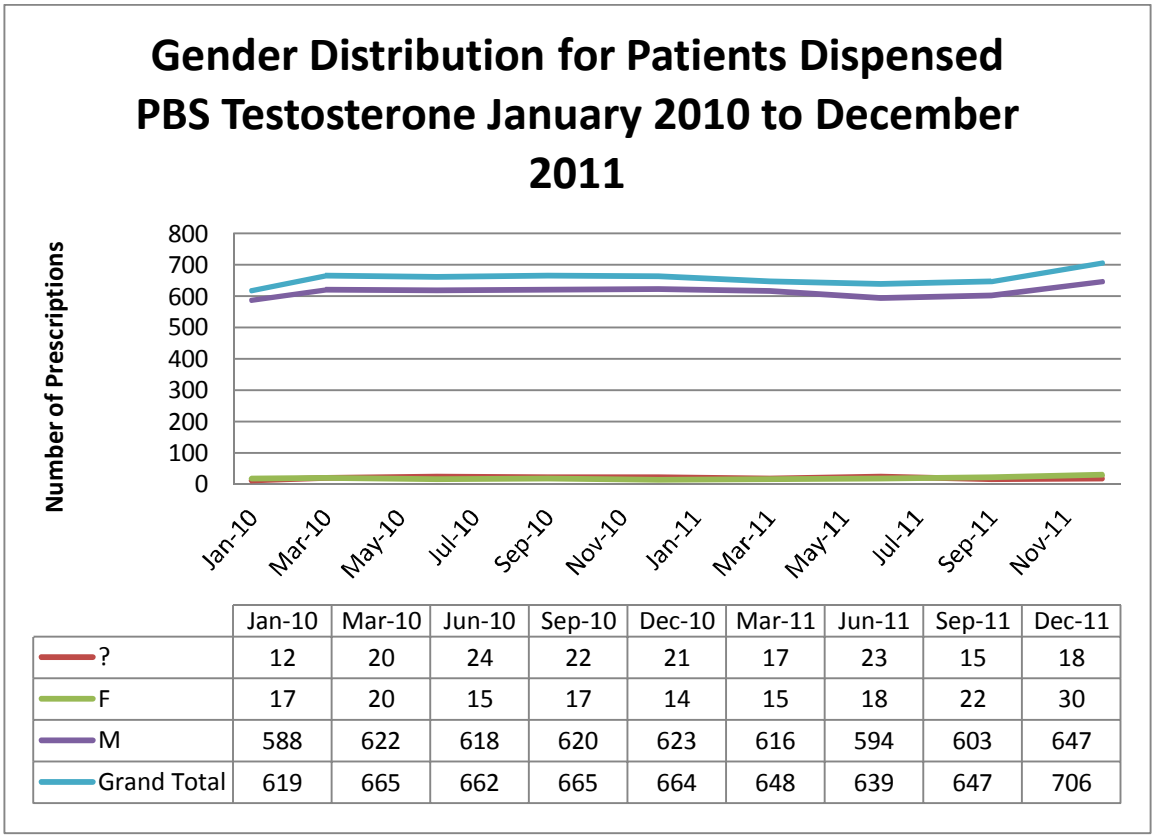


Figure 7.6.7 Proportion of patients by age initiating testosterone therapy each year.
Source: Medicare DHS, PBS Supplied Script database, extracted August 2012.

In almost all age groups, except the very young, there has been an increase in the total number of patients initiating on testosterone over time. When considered as a proportion of all initiations, most initiations are for patients aged 40-79, however within this age bracket there are some varying trends. For example the proportion of patients initiating who are aged 50-54 and 55-59 has decreased over the study period, whereas the other age groups within the 40-79 bracket have increased.



	Jan-10	Mar-10	Jun-10	Sep-10	Dec-10	Mar-11	Jun-11	Sep-11	Dec-11
?	12	20	24	22	21	17	23	15	18
F	17	20	15	17	14	15	18	22	30
M	588	622	618	620	623	616	594	603	647
Grand Total	619	665	662	665	664	648	639	647	706

Figure 7.6.8 Prescriptions of testosterone distributed by gender.
Source: Medicare DHS, PBS Supplied Script database, extracted August 2012.

In the five calendar year period between 2005 and 2011, there were 1380 testosterone prescriptions for females; this is an average of 2.8% of all testosterone scripts. This utilisation is outside of the Authority required PBS restriction. Some of these scripts may be due to data entry errors in the prescription dataset.

DUSC Secretariat Comments (for DUSC review)

- Utilisation has approximately doubled over the past 5 years. The listing of testosterone gel and long acting IM injection has driven all of the growth in the market.
- There may have been some unmet need in patients who had adverse skin reactions to patches or preferred a longer acting injection, however, as there have not been any new indications listed on the PBS for testosterone, and proportion of the additional use may not be appropriate. For example prescribing for 'andropause', the normal decline in testosterone that occurs with ageing (1).
- Testosterone initiation by GPs is increasing.

Any information provided by a drug company to DUSC or extracted from a submission to the PBAC, PBPA, used in a deed of agreement or cabinet submission is provided in-confidence.

- There are some safety concerns with testosterone. In a population of older men with limitations in mobility and a high prevalence of chronic disease, the application of a testosterone gel was associated with an increased risk of cardiovascular adverse events (2).
- Expenditure on testosterone has grown at a rate disproportionate to utilisation. The therapeutic relativities may need to be examined. Further analysis to establish the frequency of resupply of prescriptions is required.

References

1. Handlesman DJ. Pharmacoepidemiology of testosterone prescribing in Australia, 1992-2010. MJA 196 (10) 642-645, June 2012.
2. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, Eder R, Tennstedt S, Ulloor J, Zhang A, Choong K, Lakshman KM, Mazer NA, Miciek R, Krasnoff J, Elmi A, Knapp PE, Brooks B, Appleman E, Aggarwal S, Bhasin G, Hede-Brierley L, Bhatia A, Collins L, LeBrasseur N, Fiore LD, Bhasin S, 2010 Adverse events associated with testosterone administration. The New England Journal of Medicine 363:109-122

APPENDIX A

THERAPEUTIC RELATIVITY SHEETS - 1 JANUARY 2012
Extract

Testosterone esters injection 250mg and testosterone enanthate injection 250mg are considered to be approximately equivalent.

Testosterone implants were listed on the basis that 600mg every four months was similar to 250mg testosterone injection every two weeks. Testosterone transdermal patch was recommended on a cost minimisation basis compared with testosterone undecanoate capsule. The equi-effective doses are two patches 12.2mg per day and 6 capsules testosterone undecanoate 40mg per day.

Testogel®, testosterone transdermal gel 50 mg per 5 g sachet, was listed on a cost minimisation basis versus testosterone transdermal patch releasing 5 mg per day.

Reandron 1000®, testosterone undecanoate intramuscular injection was recommended on a cost minimisation basis compared to testosterone implant with the equi-effective doses being testosterone intramuscular injection 1000 mg every 12 weeks and testosterone implant (600 mg) every 4 months

APPENDIX B

DEFINED DAILY DOSE

ATC G03 – Sex Hormones and Modulators of the Genital System Effective Date: 07/10
Testosterone esters injection 250mg and testosterone enanthate injection 250mg are considered to be approximately equivalent. Testosterone implants were listed on the basis that 600mg every four months was similar to 250mg testosterone injection every two weeks. Testosterone transdermal patch was recommended on a cost minimisation basis compared with testosterone undecanoate capsule. The equi-effective doses are two patches 12.2mg per day and 6 capsules testosterone undecanoate 40mg per day.

From WHO DDD Index, Norwegian Institute of Public Health. http://www.whocc.no/

G03BA03	Name	DDD	U	Adm.R	Note
	testosterone	0.12	g	O	
		18	mg	P	
		0.12	g	R	
		3	mg	TD	
		60	mg	SL	
		50	mg	TD	gel

The DDD for parenteral and oral testosterone is expressed as declared amount of ester e.g. undecanoate.