

# Testosterone Replacement Therapy

## Pharmacoepidemiology Unit

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### Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website ([www.odprn.ca](http://www.odprn.ca)).

# Executive Summary

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## Overall National and Provincial Trends in Testosterone Use

Prescriptions for testosterone products in Canada have increased by nearly 40% over the past 4 years, from 99,854 prescriptions dispensed in the last quarter of 2009 to 137,318 prescriptions dispensed by the first quarter of 2014. The majority of testosterone prescriptions in Canada were for topical formulations (46%) followed by oral (26%), injectable (26%) and transdermal (2%) formulations. By the beginning of 2014, Ontario had the fourth-highest rate of provincially-funded prescriptions for testosterone (508 prescriptions dispensed per 100,000 eligible population compared to the national average of 489 prescriptions dispensed per 100,000 eligible population) and highest costs of provincially-funded testosterone products (\$57,519 per 100,000 eligible population compared to the national average of \$44,192 per 100,000 eligible population).

## National and Provincial Trends in Testosterone use among Public Drug Plan Beneficiaries

In 2012, Ontario had the highest provincial rate of testosterone use (1,105 users per 100,000 eligible men), overall cost (\$2 million) and highest average cost per user (\$137.5) among public drug plan beneficiaries, in Canada. This rate of use varied ten-fold across provinces, with the lowest rates observed in PEI and BC, which have more restrictive public plan listings. Injectable testosterone, which is listed as general benefit in most provinces, was the most utilized publically-funded testosterone across all provinces in Canada, except Ontario where topical testosterone use was highest. The low rates of topical testosterone utilization in provinces other than Ontario may be driven by the products having no listing (BC, Alberta, Saskatchewan, Manitoba) or enforced restricted listing (New Brunswick, Nova Scotia, PEI) compared to the unenforced restricted listing in Ontario. In Canada in 2012, the overall average cost per user for topical testosterone (\$347.4) was substantially higher than injectable testosterone (\$74.3), which may be contributing to the high average cost per user in Ontario. In 2012, Ontario had the second highest rate of testosterone use among younger (less than 65 years) and older (aged 65 and older) male beneficiaries, behind Alberta and Manitoba, respectively. Among younger male public drug plan beneficiaries in 2012, Ontario has the highest rate of oral and topical testosterone use (233 and 300 users per 100,000 eligible men, respectively) and second highest (behind Alberta) rate of injectable testosterone use (508 users per 100,000 eligible men). Among older male public plan beneficiaries, Ontario had the highest rate of topical testosterone use (327 users per 100,000 eligible men), third highest (behind Saskatchewan and Nova Scotia) rate of oral use (241 users per 100,000 eligible men) and fifth highest rate of injectable use (157 users per 100,000 eligible men) in 2012. The transdermal patch received minimal use across provinces in Canada.

## Use of Testosterone Products in Ontario

The majority of testosterone prescriptions in Ontario are paid for through private drug coverage. By the beginning of 2014, approximately 35% of prescriptions (N=16,426) were paid for through OPDP, nearly 49% (N=23,147) through private health insurance, and the remainder (17%; N=7,808) through cash payments and Non-Insured Health Benefits (NIHB). Among public drug plan beneficiaries in Ontario, testosterone use is lower among older (aged 65 and older) males compared to younger (less than 65 years) males (726 and 1,053 users per 100,000 eligible, respectively) by the end of 2012. TRT rates of use among older and younger beneficiaries have increased in Ontario, despite the introduction of

prescribing restrictions in 2006. This is largely driven by the use of topical testosterone, which was added to the provincial formulary in 2005 and increased substantially among both younger (from 50 to 300 users per 100,000 eligible men) and older (from 11 users to 327 users per 100,000 eligible men) beneficiaries, between 2005 and 2012. By the end of 2012, topical testosterone was the most utilized publically-funded testosterone among older Ontario beneficiaries, which differed from the younger population where injectable testosterone had the highest rate of use. The rate of transdermal patch testosterone has remained negligible in Ontario among both age groups.

### **Characteristics of Testosterone Users in Ontario**

In 2012, there were 6,216 younger and 8,460 older male users of provincially-funded testosterone products in Ontario. Among the younger users, the majority used injectable testosterone, lived in urban areas, had low socioeconomic status, low comorbidities and had more than 10 physician visits within the last year. Injectable testosterone users had a higher rate of health care utilization, but lower rates of comorbidities such as hypertension and diabetes, compared to the other testosterone users. Younger topical users were more likely to have HIV (14%) compared to other testosterone users (<5%). Among the older testosterone users, the majority used topical testosterone, lived in urban areas, had high socioeconomic status, more comorbidities and had less health care utilization. Older users had similar comorbidities regardless of the type of formulation used. On average, less than 15% of testosterone users had a documented diagnosis of hypogonadism according to claims data, although this varied across formulation and was highest for topical users (17%) among the younger males and injectable users (24%) among older males.

### **Patterns of Testosterone Use and Discontinuation in Ontario**

Between April 2008 and March 2013, almost half of all male beneficiaries aged 66 and older, that were new users of provincially-funded testosterone products in Ontario, were treated with topical testosterone. This was followed by oral testosterone, injectable testosterone and transdermal patch testosterone. Among new users, the majority had more than one prescription, however almost half of users initiating injectable testosterone had only one prescription. Among the patients who had more than one prescription for testosterone, adherence to therapy was highest among those prescribed oral testosterone, followed by topical testosterone, injectable testosterone and transdermal patch testosterone ( $p < 0.001$ ). A documented diagnosis of hypogonadism through claims data was low (<20%) among new testosterone users, but differed across testosterone formulation users, with patients initiating injectable formulation being more likely to have a documented diagnosis. About one-third of new testosterone users did not receive a lab test for testosterone levels in year prior to their first prescription for therapy. However, this differed by the testosterone formulation initiated, with topical and transdermal patch testosterone users more likely to have had past testosterone level lab tests in the past year compared to oral and injectable users. Testosterone users had similar comorbidities across formulation groups. The majority of new testosterone users had a diagnosis of hypertension, almost half had a past diagnosis of diabetes and the majority did not have a diagnosis of HIV.

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## Introduction

Testosterone Replacement Therapy (TRT) are drug products indicated in males for the treatment of hypogonadism. Nine testosterone products are currently available in Canada as oral, injectable, transdermal (patch) and topical (gel) formulations.

The objectives of this report are to describe national and provincial trends in the use of TRT products and to identify patterns of therapy among users with provincial drug coverage. Specifically, this report aims to:

1. Present national utilization trends of TRT in Canada, including cross-provincial comparisons of population-adjusted rates of use
2. Examine trends in indication for treatment with TRT dispensed through the Ontario Drug Benefit program
3. Describe characteristics of people treated with provincially-funded TRT in Ontario
4. Describe the characteristics of course and length of TRT among new users in Ontario

## Data Sources

### IMS Geographic Prescription Monitor (GPM<sup>12</sup>)

IMS Geographic Prescription Monitor (GPM<sup>12</sup>) is a premium source of sales intelligence on retail prescription activity in Canada. Data is obtained from a representative sample of 65% of all Canadian pharmacies and is projected monthly by province or customized geography. Projections incorporate the number of pharmacies in a given area, the distance between IMS-captured and uncaptured pharmacies, and the size of the pharmacies. Projections are representative of provincial and national sales volumes. Data available through IMS Geographic Prescription Monitor (GPM<sup>12</sup>) includes prescription volumes and units (e.g. tablets, patches) dispensed, and are stratified by payer type (e.g. public drug plan, private drug plan, cash, Non-Insured Health Benefits). Data from IMS Geographic Prescription Monitor (GPM<sup>12</sup>) is available from the fourth quarter of 2009 to the first quarter of 2014.

### Canadian Institute for Health Information NPDUIS

The National Prescription Drug Utilization Information System (NPDUIS) was developed by the Canadian Institute for Health Information (CIHI) to provide pan-Canadian information on public drug programs. NPDUIS data can be used to obtain estimates of populations eligible for provincial drug coverage in Alberta, British Columbia, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, and Prince Edward Island. Data from NPDUIS is available from 2000 to 2012.

### Ontario Drug Benefit Database

The Ontario Drug Benefit (ODB) database contains individual-level claims data for all prescription drugs dispensed to Ontario residents eligible for public drug funding. Eligibility criteria include unemployment,

disability, high prescription drug costs relative to net household income, receipt of home care services, residence in a long-term care facility, and age  $\geq$  65 years. This database is of high quality, with an error rate of  $<1\%$  and can be linked to other health administrative databases to obtain patient demographic information.<sup>1</sup> We analyzed data from the ODB between January 2000 and December 2013.

### **HIV Database**

The Ontario HIV Database contains all Ontario HIV positive patients identified since fiscal year 1992. The database was created using physician claims from the Ontario Health Insurance Plan (OHIP) claims database. The case definition for HIV uses 3 or more physician claims with an HIV diagnosis over a 3 year period ascertain prevalence, and yielded a sensitivity of 96.2% (95% confidence interval [CI] 95.2-97.9%) and specificity of 99.6% (95% CI 99.1-99.8%) when compared to chart data.<sup>2</sup>

### **Hypertension Database**

The Ontario Hypertension database contains prevalence data on all Ontario hypertension patients identified since fiscal year 1988. The database was created using hospital discharge abstracts from CIHI-DAD (including same-day surgery) and physician service claims from the OHIP claims database. The case definition for hypertension uses one or more hospitalizations with a hypertension diagnosis or an OHIP claim with a hypertension diagnosis followed within two years by either an OHIP claim or a hospital admission with a hypertension diagnosis. This database is updated every fiscal year. This algorithm was previously demonstrated to identify adults with hypertension with a sensitivity of 72%, specificity of 95%, positive predictive value of 87% and negative predictive value of 88%.<sup>3</sup>

### **Congestive Heart Failure Database**

The Ontario Congestive Heart Failure Database contains all Ontario individuals identified as having CHF since 1991. The database was created using hospital discharge abstracts from CIHI-DAD (including same-day surgery) database or the Ontario Mental Health Reporting System (OMHRS) database, physician claims from the OHIP claims database, emergency department visits from the (NACRS) and demographic information on persons eligible for health care coverage in Ontario from the Registered Persons Database (RPDB). The case definition for CHF uses one hospital admission (either from the DAD or from OMHRS) with a CHF diagnosis or an OHIP claim/NACRS ED record with a CHF diagnosis followed within one year by either a second record with a CHF diagnosis from any source. The database is re-created every fiscal year. It is assumed that once a person has been diagnosed with CHF, they will have it for the rest of their life. Prevalence is verified each year by testing whether an individual had contact with the health care system. The validation study found this algorithm to have the following sensitivity: 84.8 (77.7, 92.0) and specificity: 97.0 (96.3, 97.9).<sup>4</sup>

## **Methods**

All analyses described below were approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

## National Trends in Utilization of Testosterone Products

We used data from IMS Geographic Prescription Monitor (GPM<sup>12</sup>) to examine overall trends in the prescribing volumes of TRT including oral, topical, transdermal and injectable formulations, at both national and provincial levels. We examined the number of prescriptions dispensed for testosterone products between January 2009 and February 2014. Analyses were stratified by payer (provincially-funded vs. non-provincially-funded). Provincially-funded prescriptions were those paid for through public drug programs; non-provincially-funded prescriptions were those paid for through private insurance plans, cash payments, or Non-Insured Health Benefits (NIHB). All cross-provincial analyses compared population-adjusted rates.

### Population Adjustment – Overall Utilization

Provincial population estimates were obtained from Statistics Canada for each year from 2009 to 2013 and used to adjust the overall utilization rates (per 100,000 population) of testosterone products across the different provinces. Population counts for 2014 were estimated using linear extrapolation.

### Population Adjustment – Stratified by Payer

For measures examining provincially-funded utilization of testosterone products, we used the number of individuals eligible for provincial drug coverage in each year from 2009 to 2014 to standardize utilization rates. In the case of provinces where we had individual-level data available through NPDUI and ODB (i.e. Alberta, British Columbia, Manitoba, Saskatchewan, Ontario, New Brunswick, Nova Scotia and Prince Edward Island), we defined the number of eligible beneficiaries in each year as any individual who had at least one publically-funded drug claim over the time period. In the case of Quebec, and Newfoundland and Labrador, we obtained estimates of eligible populations from the annual reports of each public drug program. For all provinces, eligible population counts for the most recent years were estimated using linear extrapolation where data was not available.

Because all individuals (both those eligible for public drug programs and non-beneficiaries) might pay for testosterone products out of pocket, measures of non-provincially-funded utilization were adjusted using overall provincial population estimates from Statistics Canada.

## Trends in Provincially-Funded Testosterone Products in Ontario

We used claims data from ODB to perform additional analyses of utilization of testosterone products among males in Ontario, separating males under 65 and males 65 and older. These analyses included estimating the market share and costs of testosterone products as well as the number of users of publically-funded testosterone products. We also examined demographic characteristics of patients prescribed testosterone products.

## Adherence among New Users of Testosterone Replacement Therapy

We established a cohort of male patients who were new users of testosterone products between January 1, 2009 and December 31, 2012, to examine the duration of TRT in Ontario. Public drug

coverage is universal for individuals aged over 65, and we do not have complete eligibility information for younger beneficiaries. Therefore, we restricted this analysis to individuals aged 66 and older in order to ensure complete medication records and accurate ascertainment of new use of testosterone therapy. We followed each individual forward from the time of their first prescription until they discontinued therapy, died, had 2 years of follow-up or reached the end of the study period (December 31, 2013). Discontinuation of testosterone therapy was defined on the basis of no subsequent prescription for a testosterone product within 180 days of the previous prescription, which is consistent with previously published studies.<sup>5,6</sup>

## Testosterone Products in Canada

There are currently nine testosterone products marketed in Canada.

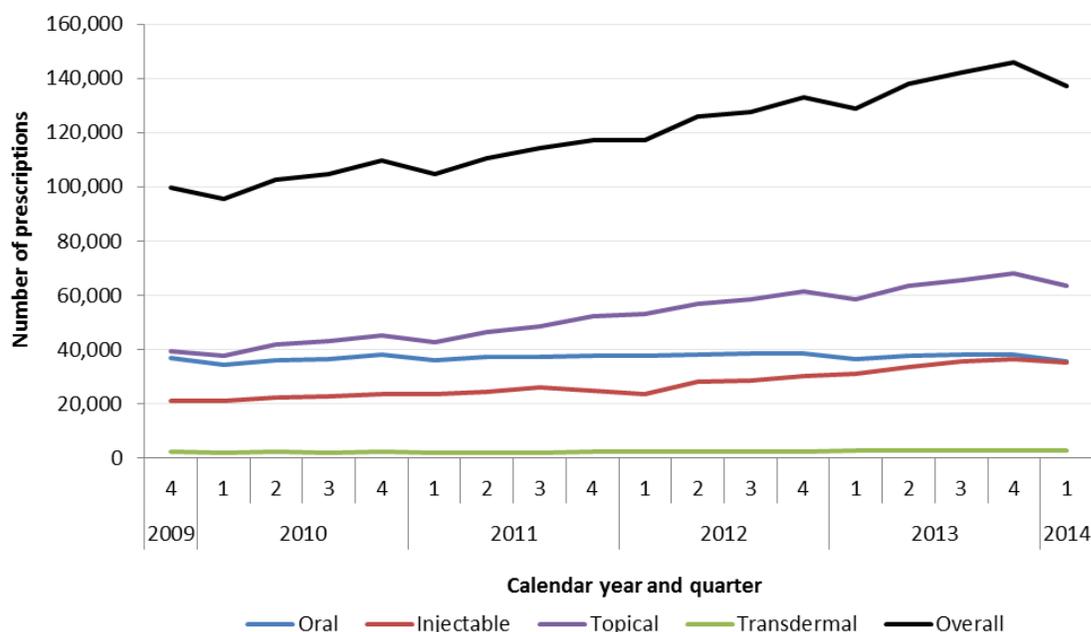
Drug	Brand name	Availability in Canada	Formulation	Ontario Public Drug Formulary Listing
Testosterone undecanoate	Andriol 40mg capsule	December 1992	Oral	Restricted (passive) <sup>1</sup>
Testosterone undecanoate	PMS-Testosterone 40 mg capsule	October 2009	Oral	Restricted (passive)
Testosterone cypionate	Depo-Testosterone 100 mg/mL	December 1953	Long-acting injectable	Restricted (passive)
Testosterone cypionate	Testosterone Cypionate Injection USP	August 2002	Long-acting injectable	Not listed
Testosterone enanthate	Delatestryl 1000mg/5mL	December 1955	Long-acting injectable	Restricted (passive)
Testosterone	Androderm 12.2mg, 24.3mg	December 2000	Transdermal patch	Restricted (passive)
Testosterone	Androgel 1% 2.5g, 5g	May 2002	Topical gel	Restricted (passive)
Testosterone	Axiron	May 2013	Topical solution	Not listed
Testosterone	Testim 1% 5g	April 2007	Topical gel	Restricted (passive)

<sup>1</sup>Restricted (passive) listing requires a patient to satisfy a Limited Use Criteria

## Exhibits and Findings

### National Trends in Utilization of Testosterone Therapies

Exhibit 1: Total utilization of TRT in Canada, by formulation and quarter



Prescriptions for testosterone products have increased by 38% over the past 4 years, largely driven by the increase in topical use. Topical testosterone products are the most commonly prescribed testosterone replacement therapy in Canada.

#### Summary of Findings for Exhibit 1

1. Testosterone utilization in Canada has increased 37.5% since Q4 2009, from a total of 99,854 prescriptions at the end of 2009 to 137,318 prescriptions by the beginning of 2014.
2. The number of prescriptions for topical and injectable testosterone has increased over the study period (61.1% and 65.2% from Q4 2009 to Q1 2014, respectively), while prescriptions for oral and transdermal patch has remained stable.
3. The prescription market share in the first quarter of 2014 was 46.4% topical (63,758 prescriptions), 26% oral (35,653 prescriptions), 25.5% injectable (35,073 prescriptions), and 2.1% transdermal patch (2,834 prescriptions).
4. By the end of the study period, topical testosterone had the highest quarterly costs (\$9.8 million in Q1 2014) in Canada.
5. By the first quarter of 2014, a total of \$14.2 million was spent on all testosterone products nationally, an increase of approximately 42.1% since Q4 2009 (\$10 million). Among the total cost of testosterone prescriptions in Q1 2014, the majority was spent on topical formulations (69.4%; \$9.8 million), followed by oral (17.5%; \$2.5 million) injectable (10.8%; \$1.5 million) and patch (2.3%; \$322,220) formulations (data not shown).
6. A decline in the number of prescriptions and costs for TRT observed in Q1 2014 may be due to cardiovascular concerns that prompted a re-evaluation of the drug class by Health Canada.

## Population-adjusted rates of Testosterone utilization, by funding type

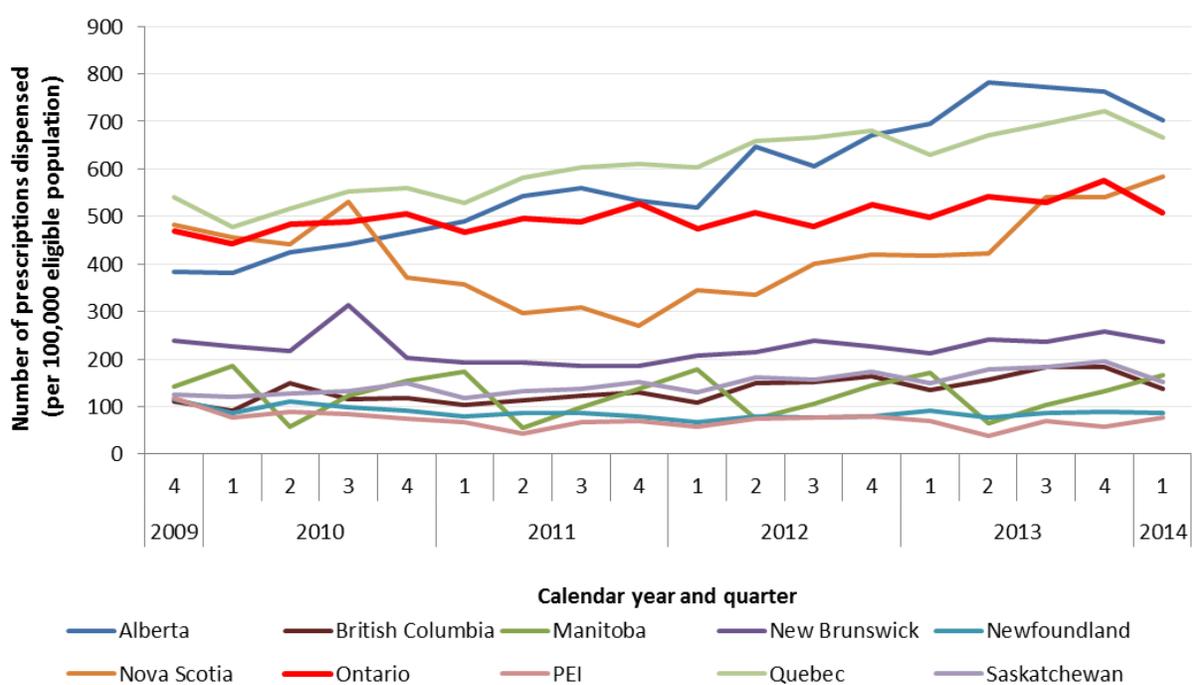
### Methodological Note:

Non-provincially-funded use represents use outside of provincial drug plans. This includes prescriptions paid by:

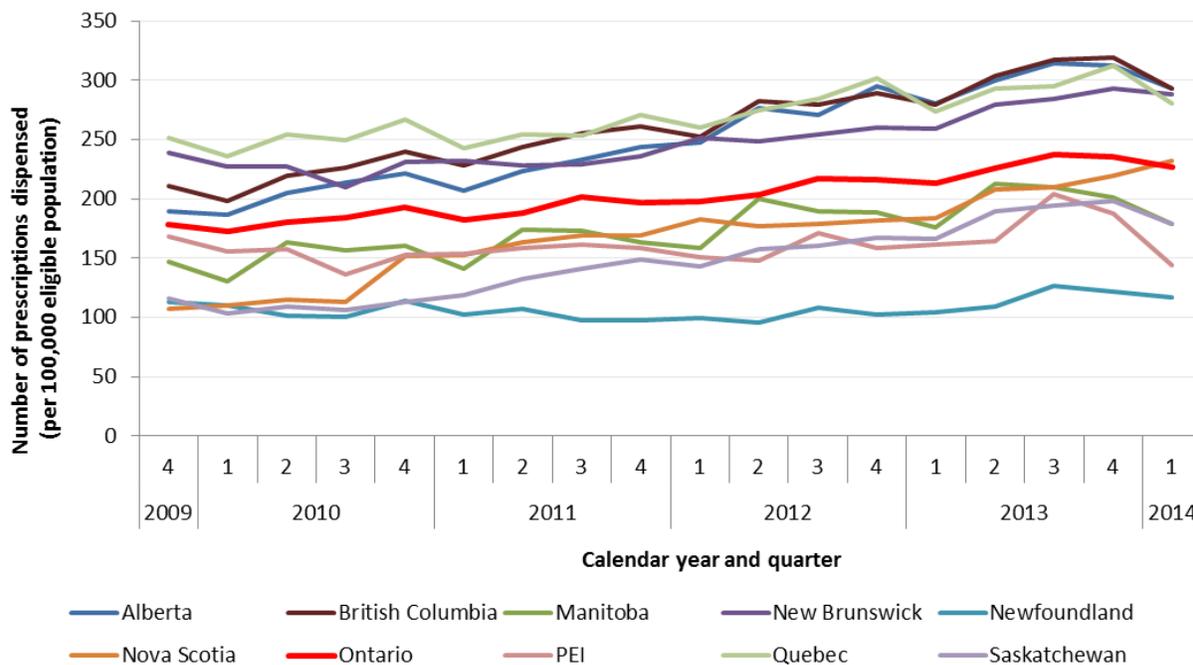
- Private drug insurance
- Cash
- Non-Insured Health Benefits

Public plan listings for Testosterone products vary across the provinces and formulation. Detailed information on public plan listings is provided in Appendix A.

Exhibit 2: Population-adjusted utilization of provincially-funded testosterone in Canada by province



**Exhibit 3: Population-adjusted utilization of non-provincially funded testosterone in Canada by province**



Ontario has the third highest rate of prescriptions for provincially-funded testosterone products over the study period, in Canada.

### Summary of Findings for Exhibit 2 and Exhibit 3

1. There was wide variation in the number of provincially-funded testosterone prescriptions dispensed between provinces (from 76 [PEI] to 702 [Alberta] prescriptions per 100,000 eligible population, in Q1 2014). The low rate of testosterone prescriptions in other provinces may reflect the restrictive access of these medications through the public drug program.
2. Cross-provincial variations were also noted among non-provincially-funded products (from 117 [Newfoundland] to 293 [Alberta and British Columbia] prescriptions per 100,000 eligible population, in Q1 2014).
3. By the first quarter of 2014, Ontario had the fourth highest rate of provincially-funded testosterone use (508 prescriptions per 100,000 eligible population compared to the national average of 489 prescriptions per 100,000 eligible population) and highest costs of provincially-funded testosterone products (\$57,519 per 100,000 eligible population compared to the national average of \$44,192 per 100,000 eligible population (data not shown)). This may be due to the high use of topical testosterone in Ontario, which is the most costly testosterone formulation.
4. Non-provincially-funded testosterone use in Ontario was on par with the national average (226 prescriptions per 100,000 eligible population compared to the national average of 252 prescriptions per 100,000 eligible population in Q1 2014).

## Population-adjusted rates of Testosterone utilization, among public plan beneficiaries

### Methodological Note:

The following analyses are conducted using public drug beneficiary data collected by the Canadian Institute for Health Information and ICES. No data was available for Quebec and Newfoundland & Labrador

### Exhibit 4: Characteristics of testosterone use among public drug program beneficiaries in 2012, by province

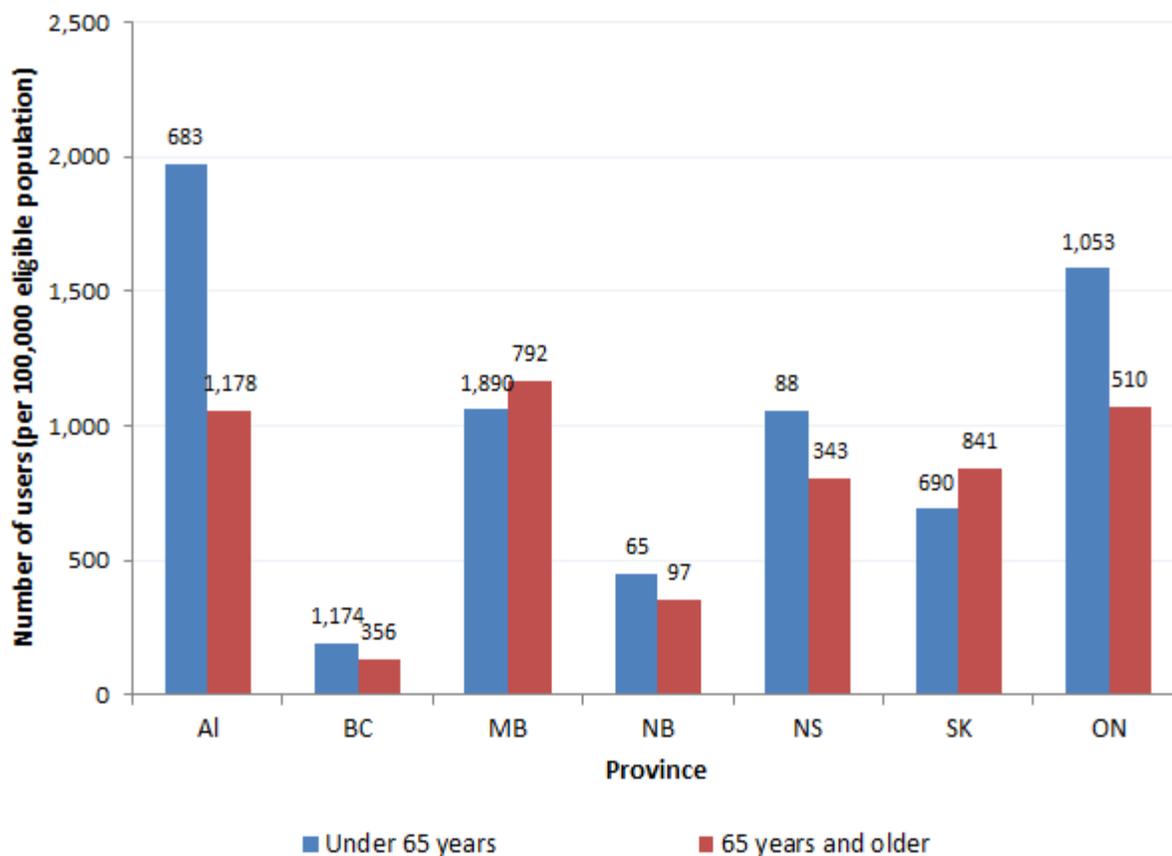
PROVINCE	# OF MALE TESTOSTERONE PATIENTS	# OF ELIGIBLE MEN	RATE OF USE (PER 100,000 ELIBLE MEN)	AVERAGE AGE
Alberta	2,461	223,977	1,099	67
British Columbia	1,530	1,182,326	129	54
Manitoba	2,682	316,033	849	56
New Brunswick	162	47,930	338	64
Nova Scotia	431	55,866	771	68
Prince Edward Island	14	14,044	100	48
Saskatchewan	1,563	269,918	579	58
Ontario	14,701	1,330,833	1,105	61

Testosterone utilization rates vary ten-fold among male drug plan beneficiaries, with the lowest rates in Prince Edward Island and the highest rates in Ontario in 2012.

### Summary of Findings for Exhibit 4

1. Testosterone utilization among male public drug plan beneficiaries varies, with the lowest rates in PEI and British Columbia (100 and 129 per 100,000 eligible men, respectively) and the highest rates in Alberta and Ontario (1,099 and 1,105 per 100,000 eligible men, respectively) in 2012. This variation may reflect provincial differences in public plan listings and the criteria restricting use of testosterone products (Appendix A). For example, injectable testosterone is the only formulation publically listed in British Columbia, and is only available under enforced restricted access, while Ontario has oral, injectable, topical, and transdermal patch formulations available under unenforced restricted access.
2. The average age of active male beneficiaries was lowest in PEI (48 years of age) and highest in Alberta and Nova Scotia (67 and 68 years of age, respectively) in 2012.

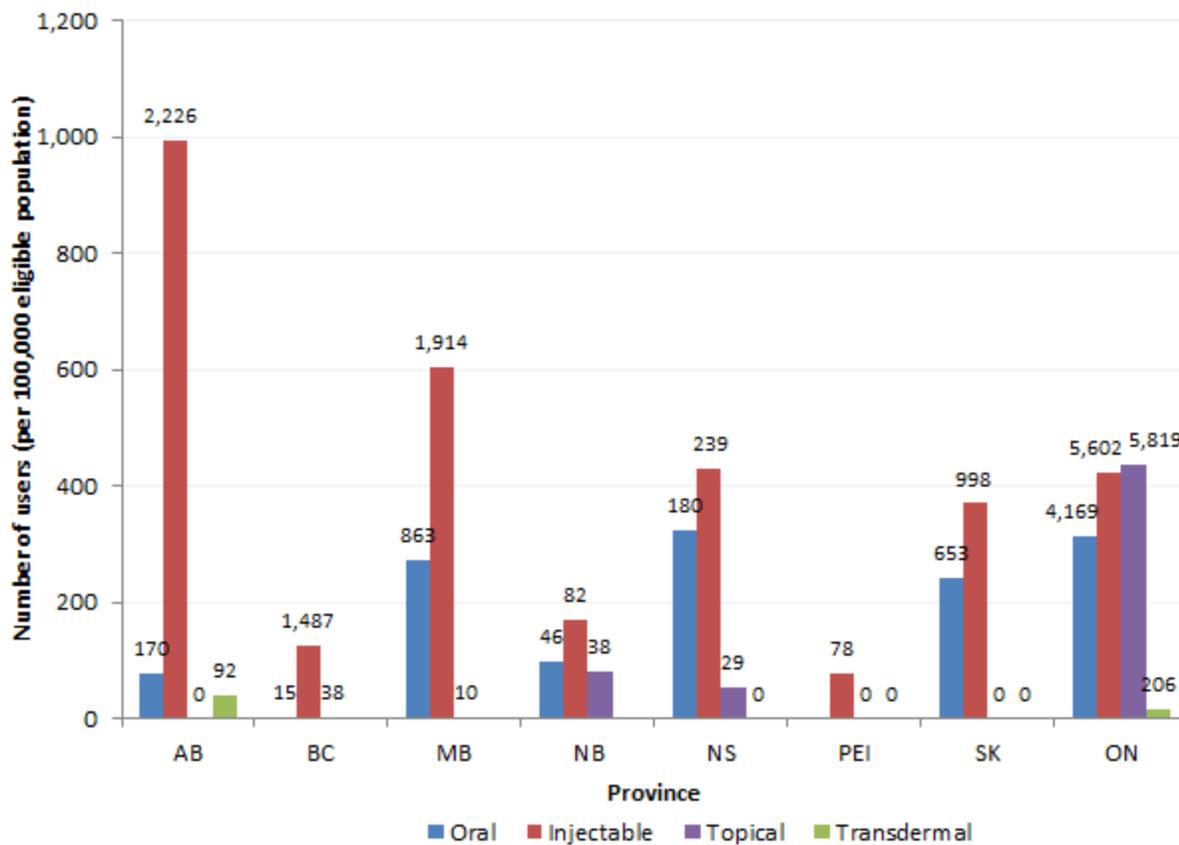
Exhibit 5: Rate of testosterone use among public drug plan beneficiaries in 2012, by age and province



Legend: Bars indicate the population adjusted rate of testosterone utilization. The number of testosterone users is displayed above each bar. Data for Prince Edward Island is not available due to small cell counts.

Older male beneficiaries (65+) have higher testosterone utilization rates than younger male beneficiaries (<65) in provinces with fewer access restrictions on testosterone use.

Exhibit 6: Rate of testosterone use among public drug plan beneficiaries in 2012, by formulation and province



Legend: Bars indicate the population adjusted rate of testosterone utilization. The number of testosterone users is displayed above each bar. Where the number of users is not indicated, data was not available or was censored due to small cell counts.

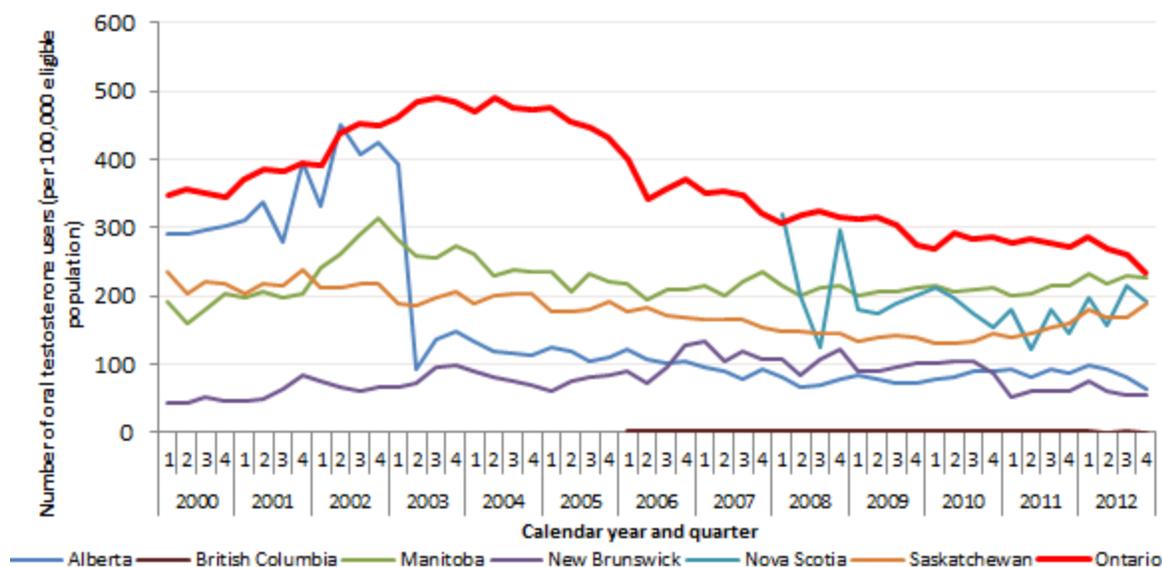
In 2012, injectable testosterone utilization rates were higher than other formulation rates in all Canadian provinces studied except for Ontario, where topical rates were highest.

### Summary of Findings for Exhibit 5 and Exhibit 6

1. In 2012, the rate of testosterone users was higher among younger (<65) vs. older (65+) male beneficiaries in provinces with restrictions on the use of testosterone products (Alberta, 1,972 vs. 1,055; British Columbia, 189 vs. 132; New Brunswick, 447 vs. 352; Nova Scotia, 1,057 vs. 804 and Ontario, 1,585 vs. 1,071 users per 100,000 eligible men, respectively). Manitoba and Saskatchewan, where there are no restrictions for injectable or oral testosterone products (but topical/patch products are not listed), had lower utilization rates of use for younger vs. older male beneficiaries (Manitoba, 1,059 vs. 1,179 and Saskatchewan, 690 vs. 841 users per 100,000 eligible men, respectively).
2. The rate of injectable testosterone use is highest among all formulations in all provinces across Canada (ranging from 78 users in PEI to 994 users in Alberta per 100,000 eligible men), with the exception of Ontario.
3. Topical and injectable testosterone rates of use were the highest in Ontario (437 and 421 users per 100,000 eligible men, respectively) in 2012. This may be driven by Ontario's passive restricted listing of these drugs on the formulary.
4. The testosterone transdermal patch received minimal use compared to the other formulations, with the majority of use in Alberta and Ontario in 2012 (41 and 15 users per 100,000 eligible men, respectively).
5. The lower rates of topical testosterone utilization in provinces other than Ontario may be explained by lack of product listing (British Columbia, Alberta, Saskatchewan, Manitoba) or more restricted listings (New Brunswick, Nova Scotia, Prince Edward Island).

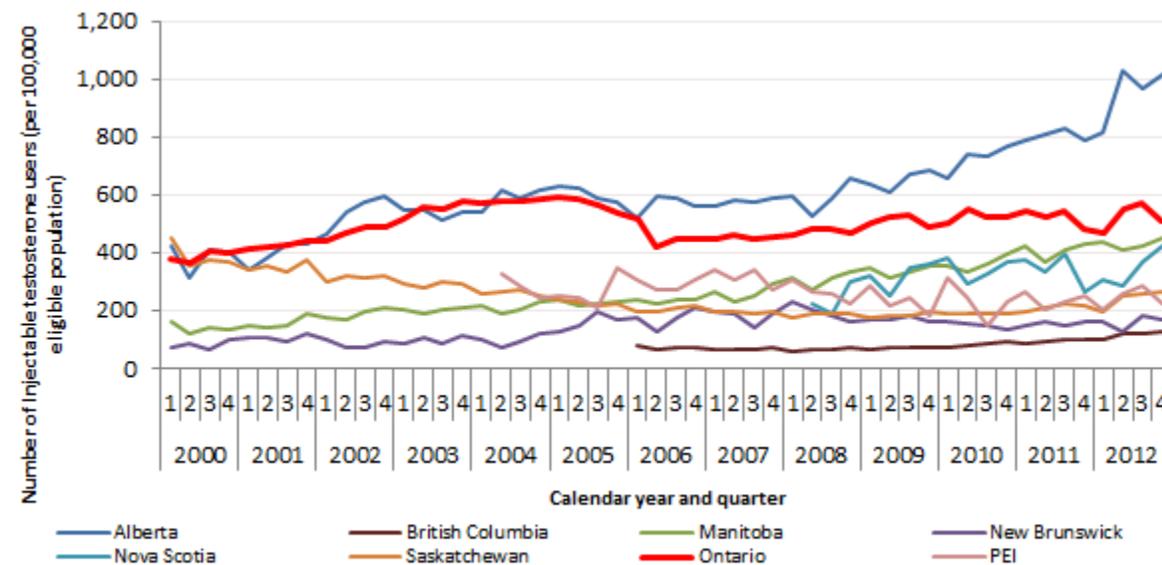
Rate of Testosterone Use, by Age

Exhibit 7: Rate of oral testosterone use among public drug plan beneficiaries less than 65 years of age, by province



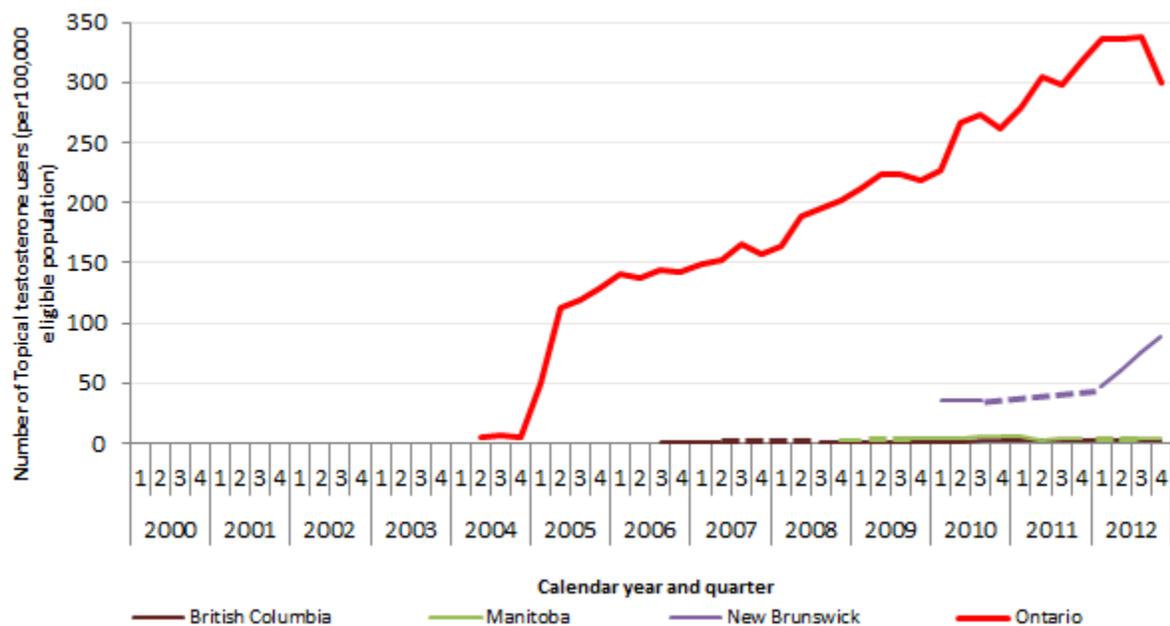
Legend: Data was not available or suppressed for British Columbia prior to 2005 and for PEI throughout the study period due to small cell counts.

Exhibit 8: Rate of injectable testosterone use among public drug plan beneficiaries less than 65 years of age, by province



Legend: Data was not available or suppressed for British Columbia prior to 2005 and for PEI prior to 2004 due to small cell counts.

**Exhibit 9: Rate of topical testosterone use among public drug plan beneficiaries less than 65 years of age, by province**



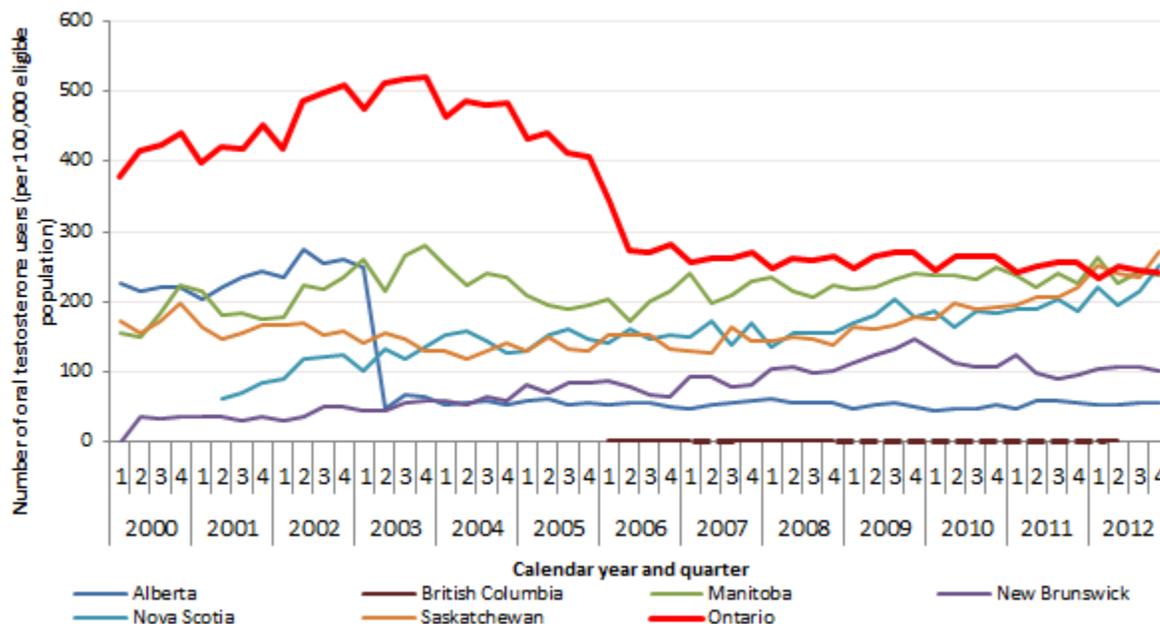
*Legend: Dashed line represents time when British Columbia, Manitoba, and New Brunswick data not available or censored due to small cell counts. Data was not available for Nova Scotia due to small cell counts.*

Ontario has the highest rate of oral and topical testosterone use among younger public drug plan beneficiaries, with declining oral use and rapidly increasing topical use over time. Ontario has the second highest (behind Alberta) rate of use for injectable testosterone is second highest (behind Alberta) in Canada.

### Summary of Findings for Exhibit 7, Exhibit 8, and Exhibit 9

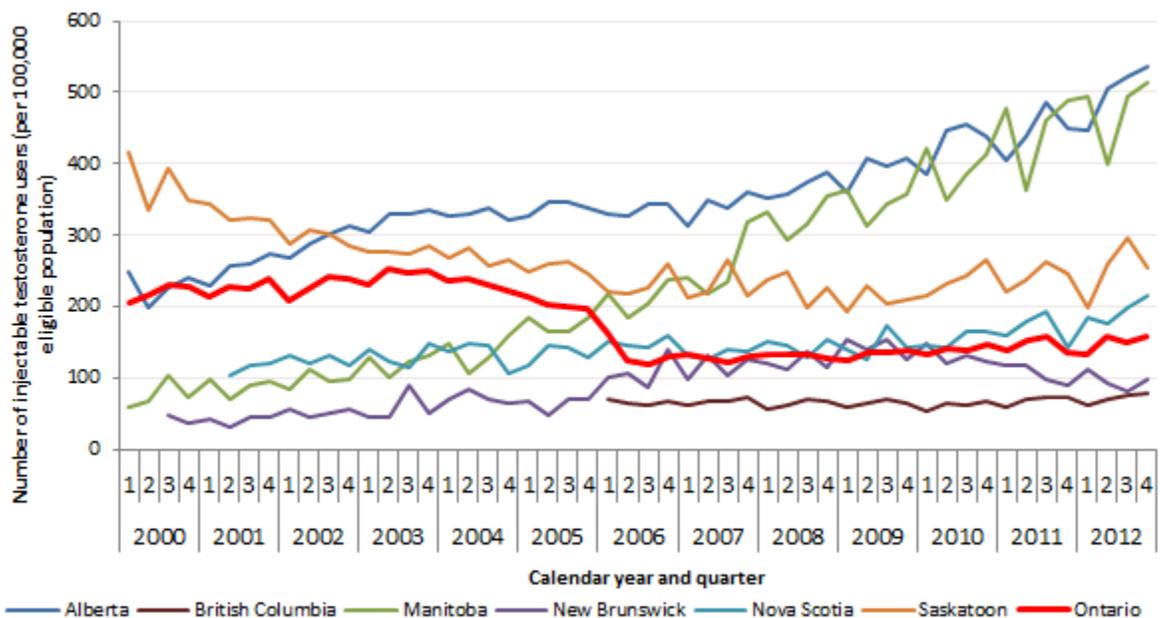
1. Following the introduction of universal prescribing restrictions for testosterone in Ontario in early 2006 (i.e., Limited Use code) oral and injectable testosterone utilization initially declined by approximately 20% (431 to 343 users and 540 to 420 users per 100,000 eligible men, respectively, from Q4 2005 to Q2 2006). Oral testosterone utilization rates continued to decline to 233 users per 100,000 eligible men by Q4 2012 while injectable testosterone utilization rates slowly increased to 508 users per 100,000 eligible men by Q4 2012.
2. Among younger beneficiaries, injectable testosterone use increased in all provinces except Saskatchewan and PEI, with the highest rate of use in Alberta (138% increase from 425 to 1,013 per 100,000 eligible men over 12 years). Saskatchewan and PEI exhibited rates decreasing by 42% (from 454 in Q1 2000 to 263 in Q4 2012 per 100,000 eligible men) and 31% (from 326 in Q2 2004 to 226 in Q4 2012 per 100,000 eligible men).
3. When prescribing restrictions were introduced for oral testosterone products in Alberta in 2003, oral testosterone utilization rates for younger public drug plan beneficiaries decreased by 77% (from 393 in Q1 2003 to 92 in Q2 2003 per 100,000 eligible men) with rates stabilizing thereafter.
4. Topical testosterone utilization rates for younger male beneficiaries in Ontario rapidly increased 60-fold over a ten year period (from 5 users in Q2 2004 to 300 users in Q4 2014 per 100,000 eligible men), aligning with the entry of topical testosterone to the provincial formulary in 2005. Topical utilization rates are negligible in Nova Scotia, PEI, and Newfoundland even though topical drugs are listed.
5. Rates of testosterone transdermal patch use among younger beneficiaries were highest in Alberta (69 users per 100,000 eligible men) and Ontario (11 users per 100,000 eligible men) at the end of 2012. Utilization is negligible in the other provinces where the transdermal patch was listed (New Brunswick and Nova Scotia; data suppressed due to small cell counts).

**Exhibit 10: Rate of oral testosterone use among public drug plan beneficiaries 65 years of age or older, by province**

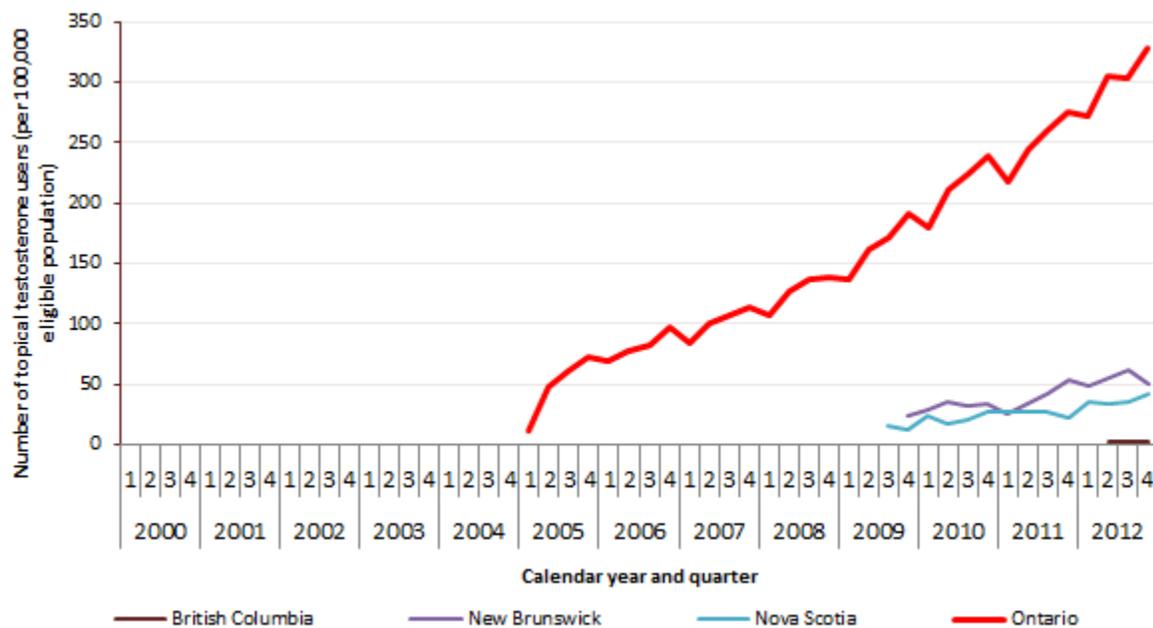


Legend: Dashed line represents time when British Columbia data not available or censored due to small cell counts.

**Exhibit 11: Rate of injectable testosterone use among public drug plan beneficiaries 65 years of age or older, by province**



**Exhibit 12: Rate of topical testosterone use among public drug plan beneficiaries 65 years of age or older, by province**



Trends in oral and topical testosterone use were similar between older and younger public drug plan beneficiaries within provinces, with declining oral use and rapidly increasing topical use over time. Ontario had the third highest (behind Alberta and Manitoba) utilization rate of injectable testosterone use by 2012 in older beneficiaries.

### Summary of Findings for Exhibit 10, Exhibit 11, and Exhibit 12

1. Cross-provincial trends in oral testosterone utilization rates were similar between younger (<65) and older (65+) beneficiaries by the end of 2012.
2. Oral testosterone utilization rates for older beneficiaries were lowest in Alberta and New Brunswick where oral testosterone drugs are under enforced restricted listing (57 and 102 users per 100,000 eligible men, respectively), and highest in Saskatchewan, Nova Scotia, Ontario, and Manitoba, where drugs have unrestricted or passive restricted listing (270; 251; 241; 238 per 100,000, respectively by the end of 2012).
3. Similar to the younger beneficiaries, oral testosterone utilization rates among older beneficiaries substantially decreased in Alberta by 81% from Q1 2003 to Q2 2003 and Ontario by 44% from Q4 2005 to Q2 2006 following the introduction of prescribing restrictions on oral testosterone products in Alberta and all testosterone products in Ontario.
4. Injectable testosterone use among older public drug plan beneficiaries increased in Alberta, Manitoba, New Brunswick, and Nova Scotia, with rates of use highest in Alberta and Manitoba at the end of 2012 (536 and 512 users per 100,000 eligible men, respectively). Following the introduction of universal testosterone prescribing restrictions in Ontario, older beneficiaries experienced a steeper decline in utilization rates of 38% (from 198 to 124 users per 100,000 eligible men between Q4 2005 and Q2 2006) followed by stable utilization rates whereas younger beneficiaries experienced an initial decline of 22% followed by modestly increasing utilization rates. At the end of 2012, Ontario had the fifth lowest rate of injectable testosterone use (157 users per 100,000 eligible) in Canada.
5. The rate of topical testosterone use was highest in Ontario by the end of 2012. Trends in topical testosterone utilization rates in older beneficiaries were similar to younger beneficiaries in Ontario, rapidly increasing 29-fold over a 7 year period (from 11 users in Q1 2005 to 327 users in Q4 2012 per 100,000 eligible men). By the end of 2012, topical testosterone utilization rates in Ontario were similar between younger and older beneficiaries (300 and 327 per 100,000 eligible men, respectively).
6. By the end of 2012, the testosterone transdermal patch utilization rate among older beneficiaries in Alberta and Ontario was 21 and 7 per 100,000 eligible men, respectively, about half of the rate of use in younger beneficiaries (data not shown). Data was not available for New Brunswick or Nova Scotia due to small cell counts.

## Testosterone Costs, Overall and Per Person

**Exhibit 13: Overall cost of average cost per user of testosterone for last quarter of 2012, by age, formulation and province**

AGE	PROVINCE	OVERALL COST**	AVG COST PER USER**	BY FORMULATION					
				ORAL		INJECTABLE		TOPICAL	
				OVERALL COST	AVG COST PER USER	OVERALL COST	AVG COST PER USER	OVERALL COST	AVG COST PER USER
<65	Alberta	\$71,753.34	\$105.06	\$ 8,263.85	\$375.63	\$52,591.75	\$149.83	0	NA†
	British Columbia	\$68,974.34	\$58.75	\$1,448.53	\$289.71	\$61,914.11	\$78.87	\$5,611.7	\$374.11
	Manitoba	\$175,121.30	\$92.66	\$ 107,782.71	\$266.79	\$63,918.42	\$79.50	\$3,420.17	\$488.60
	New Brunswick	\$7,751.34	\$119.25	\$1,660.90	\$207.61	\$1,593.45	\$63.74	\$4,496.99	\$345.92
	Nova Scotia	*	*	\$3,605.57	\$225.35	\$2,399.27	\$68.55	*	*
	Saskatchewan	\$96,570.61	\$91.71	\$66,411.98	\$229.80	\$30,158.63	\$75.21	0	NA†
	Ontario	\$673,714.57	\$108.14	\$151,960.22	\$165.90	\$139,460.04	\$69.87	\$371,516.08	\$314.84
65+	Alberta	\$95,214.03	\$53.55	\$31,499.73	\$328.12	\$7,6732.4	\$84.97	0	NA†
	British Columbia	\$20,652.40	\$58.01	\$1,368.12	\$273.62	\$15,992.77	\$74.04	\$3,291.51	\$411.44
	Manitoba	\$64,674.27	\$81.66	\$39,968.45	\$248.25	\$24,705.82	\$71.20	0	NA†
	New Brunswick	\$13,713.66	\$141.38	\$6,073.38	\$216.91	\$1,604.46	\$59.42	\$6,035.82	\$431.13
	Nova Scotia	\$34,544.65	\$100.71	\$21,629.9	\$202.15	\$7,016.96	\$76.27	\$5,897.79	\$327.66
	Saskatchewan	\$49,428.80	\$96.92	\$38,167.14	\$232.73	\$11,261.66	\$73.13	0	NA†
	Ontario	\$1,347,207.70	\$159.04	\$328,560.91	\$172.29	\$73,934.44	\$59.39	\$931,848.88	\$360.07

†No active beneficiaries for this group.

\* Data not available or censored due to small cell counts.

\*\*Includes oral, injectable, topical, and transdermal patch costs.

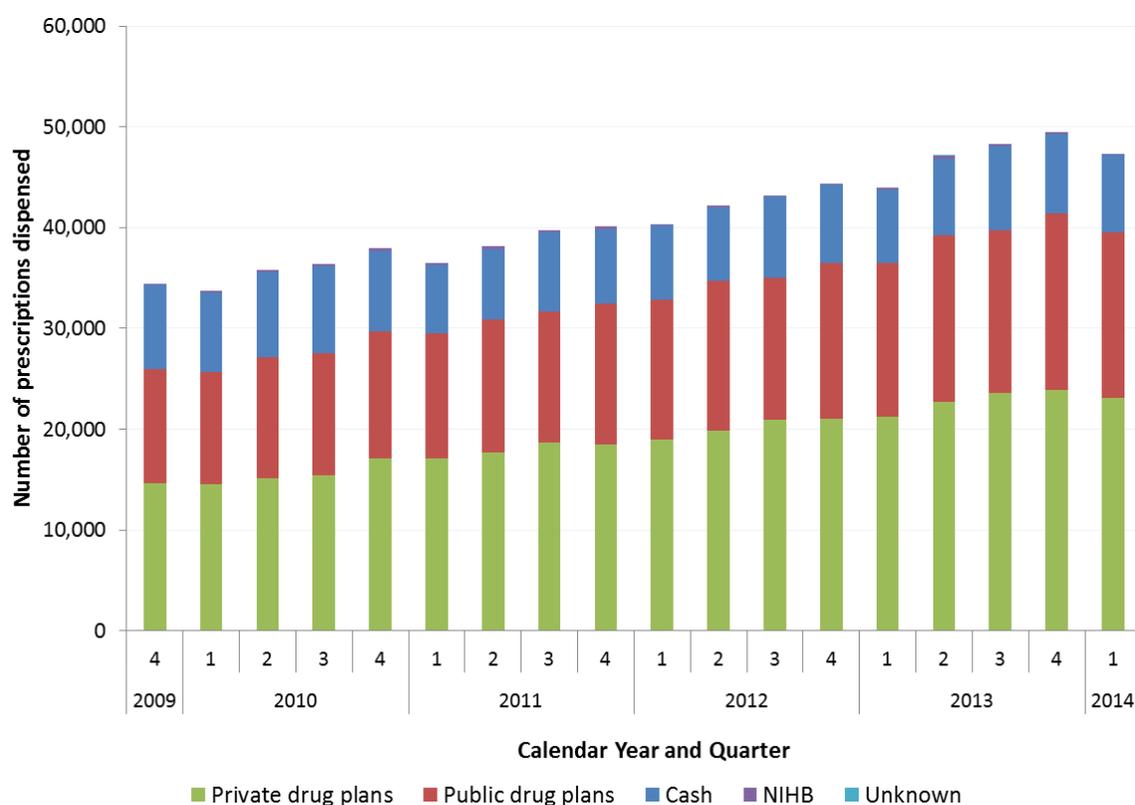
In the last quarter of 2012, Ontario's total public drug plan costs were the highest among all provinces for both age groups, with the highest average cost per user among older beneficiaries and the second highest (after New Brunswick) average cost per user in younger beneficiaries.

### Summary of Findings for Exhibit 13

1. Ontario has the highest total public drug plan costs, which were twice as high for older beneficiaries (\$1.4 million) than for younger beneficiaries (\$673,715) at the end of 2012.
2. Ontario also has the highest average cost per user among older beneficiaries (\$159.0) and the second highest (after New Brunswick) average cost per user among younger beneficiaries (\$108.1).
3. The overall average cost per user for topical testosterone products (\$347.4) was highest compared to oral (\$195.5) and injectable (\$74.3) costs per user in the last quarter of 2012 (data not shown).
4. In 2012, Ontario's average public drug plan costs per user were lower compared to other provinces except for the injectable drugs in younger beneficiaries (\$69.87 vs. \$63.74 in New Brunswick) and the topical drugs in older beneficiaries (\$360.07 vs. \$327.66 in Nova Scotia).
5. Following the introduction of the generic PMS-testosterone drug in 2009, the average cost per user of oral testosterone drugs among both younger and older public drug plan beneficiaries decreased by approximately 39% in Ontario between Q4 2009 and Q4 2012 (from \$270.8 to \$165.6 and \$281.3 to \$172.3, respectively), but remained steady in other provinces (data not shown).
6. Alberta had the highest average cost per user for injectable testosterone among younger and older beneficiaries, which increased to \$149.9 and \$85.0, respectively, by the end of 2012. Other provinces also experienced this increase, but to a lesser extent; the average cost per user increased in Ontario from \$44.8 to \$69.9 for younger beneficiaries and \$35.7 to \$59.4 for older beneficiaries from the start of 2000 to the end of 2012 (data not shown).

## Trends in Provincially-Funded Testosterone Products in Ontario

Exhibit 14: Total utilization of testosterone products in Ontario, by coverage



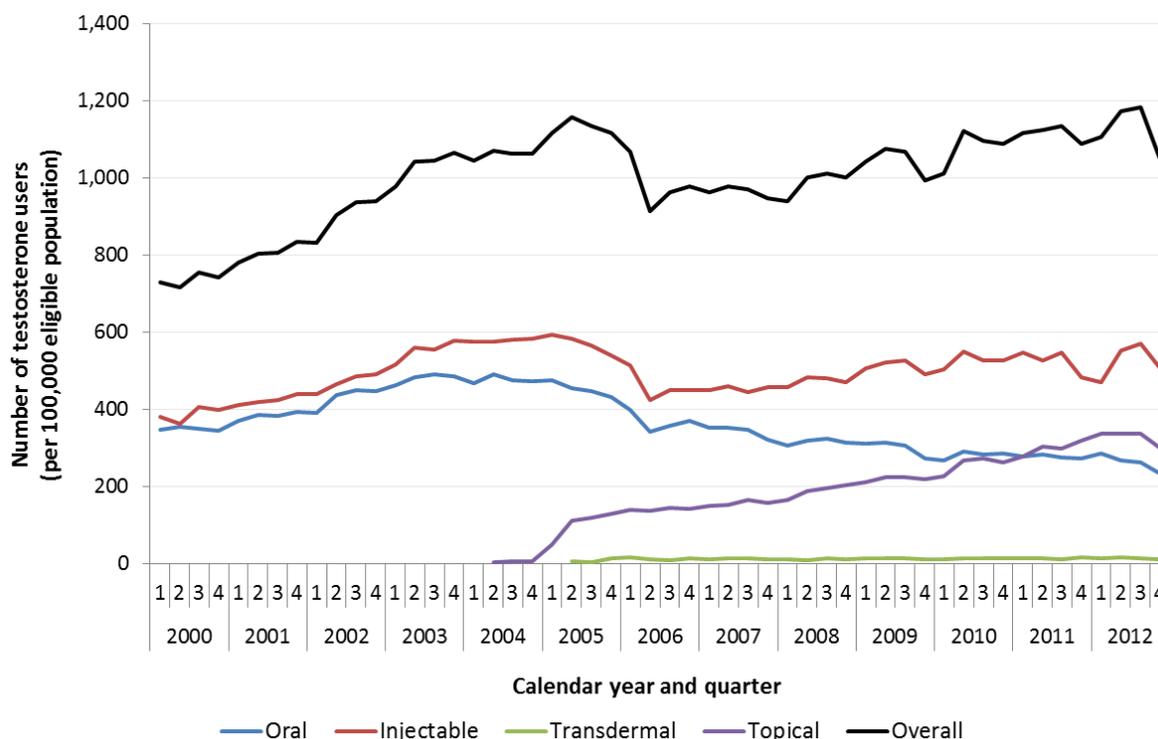
34.7% of testosterone products were paid for by the Ontario Public Drug Program in the first quarter of 2014. The majority of testosterone products are paid for by private drug plans (48.9%).

### Summary of Findings for Exhibit 14

1. The number of testosterone prescriptions dispensed in Ontario has increased 38.0%, from 34,467 prescriptions at the end of 2009 to 47,381 prescriptions at the beginning of 2014.
2. The majority of testosterone prescriptions dispensed in Ontario are paid by private drug plans, which increased 58.4% from 14,612 prescriptions in Q4 2009 to 23,147 prescriptions in Q1 2014.
3. A lower proportion of testosterone prescriptions are paid for by cash or Non-Insured Health Benefits (NIHB), which has decreased from 24.7% in Q4 2009 to 16.5% in Q1 2014.
4. By the beginning of 2014, the distribution of payers for testosterone prescriptions dispensed in Ontario was 48.9% private, 34.7% public, 16.2% cash and 0.3% Non-Insured Health Benefits (NIHB).

## Rate of Testosterone Use, by Age

Exhibit 15: Rate of testosterone use among public drug plan beneficiaries less than 65, in Ontario

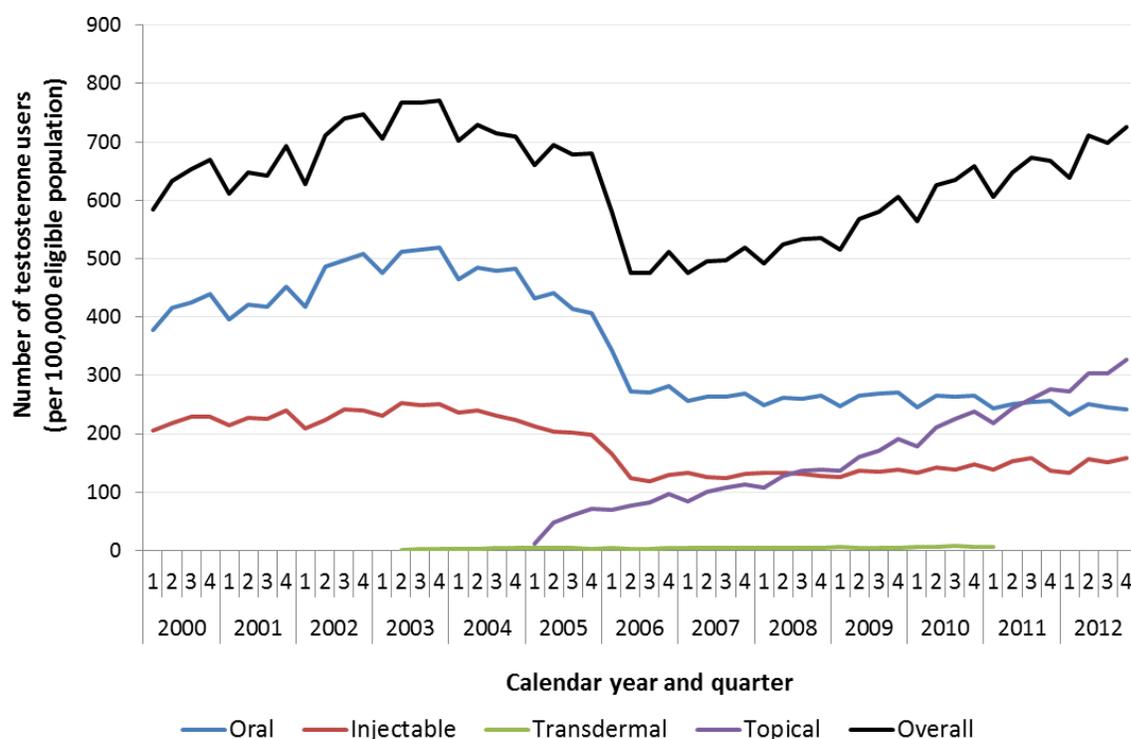


The overall testosterone rate of use among younger men in Ontario has increased over time, largely driven by the increasing use of topical formulations. By the end of 2012, injectable testosterone was the most utilized publically-funded testosterone formulation.

### Summary of Findings for Exhibit 15

1. The rate of testosterone use among younger men (<65) in Ontario has increased 44% from the beginning of 2000 to the end of 2012 (730 to 1,053 users per 100,000 eligible men), despite a 18% decline in the rate of use in the first half of 2006 (from 1,116 users in Q4 2005 to 915 users in Q2 2006 per 100,000 eligible men) when the universal prescribing restrictions for testosterone use was introduced in Ontario.
2. The rate of injectable testosterone use has increased 33% over the study period (from 382 users in Q1 2000 to 508 users in Q4 2012 per 100,000 eligible men), despite a decline of 22% at the beginning of 2006 (from 540 users in Q4 2005 to 423 users in Q2 2006 per 100,000 eligible men). By the end of 2012, injectable testosterone remained the most utilized publically-funded testosterone formulation among the younger male beneficiaries in Ontario.
3. The rate of oral testosterone has declined by 33% over the study period from 348 to 233 users per 100,000 eligible men.
4. Topical testosterone rate of use has increased markedly over the study period, from 5 users in Q2 2004 to 300 users at the end of 2012, per 100,000 eligible men.
5. The rate of transdermal patch testosterone use has remained low in Ontario with 7 users per 100,000 eligible men by the end of 2012, despite being having a passive restricted listing on the formulary.

**Exhibit 16: Rate of testosterone use among public drug plan beneficiaries aged 65 and older, in Ontario**



The overall testosterone rate of use among older men in Ontario has also increased at a lower rate over time compared to younger men. This growth has largely been driven by the availability and increasing rate of topical testosterone use, which is the most utilized publicly-funded testosterone formulation by the end of 2012.

#### Summary of Findings for Exhibit 16

1. Use of testosterone products among older men (65+) in Ontario has increased 24% over the study period, (from 583 to 726 users per 100,000 eligible men), despite a 30% decline in the rate of use in the first half of 2006 when prescribing restrictions were introduced.
2. Rates of oral and injectable testosterone use decreased between the beginning of 2000 and end of 2012 by 36% (from 378 to 241 users per 100,000 eligible men) and 24% (from 206 to 158 users per 100,000), respectively. This was driven largely by a decline in use with the prescribing restrictions in 2006 with rate of use remaining steady afterwards.
3. Similar to the younger population, topical testosterone rate of use has increased markedly over the study period, from 11 users in Q1 2005 to 327 users in Q4 2012, per 100,000 eligible men. By the end of 2012, topical testosterone was the most utilized publicly-funded testosterone among older Ontario beneficiaries, which differed from the younger population where injectable testosterone had the highest rate of use.
4. The rate of use for transdermal testosterone has remained negligible in Ontario.

## Characteristics of users of provincially-funded Testosterone products in Ontario

Exhibit 17: Baseline characteristics of provincially-funded testosterone users under 65 in Ontario, by formulation, calendar year 2012

	Overall	Oral	Topical	Transdermal	Injectable
<b>Number of testosterone users</b>	<b>6,216</b>	<b>1,309</b>	<b>1,757</b>	<b>75</b>	<b>3,075</b>
<b>Age</b>					
Median (IQR)	47.5 (37.0-55.4)	49.5 (41.5-56.9)	50.1 (40.9-57.4)	51.9 (43.1-56.4)	44.4 (34.4-53.4)
<45	2,656 (42.7%)	454 (34.7%)	587 (33.4%)	21 (28.0%)	1,594 (51.8%)
45-54	1,930 (31.1%)	448 (34.2%)	588 (33.5%)	31 (41.3%)	863 (28.1%)
55-64	1,630 (26.2%)	407 (31.1%)	582 (33.1%)	23 (30.7%)	618 (20.1%)
<b>Urban Residence</b>	5,484 (88.2%)	1,121 (85.6%)	1,582 (90.0%)	58 (77.3%)	2,723 (88.6%)
<b>LTC Resident</b>	23 (0.4%)	*	≤5	0 (0.0%)	12 (0.4%)
<b>Socioeconomic status</b>					
<i>Q1 (lowest)</i>	2,249 (36.18%)	470 (35.91%)	629 (35.80%)	18 (24.00%)	1,132 (36.81%)
<i>Q2</i>	1,316 (21.17%)	302 (23.07%)	339 (19.29%)	15 (20.00%)	660 (21.46%)
<i>Q3</i>	1,023 (16.46%)	211 (16.12%)	300 (17.07%)	17 (22.67%)	495 (16.10%)
<i>Q4</i>	868 (13.96%)	168 (12.83%)	268 (15.25%)	11 (14.67%)	421 (13.69%)
<i>Q5 (highest)</i>	723 (11.63%)	150 (11.46%)	216 (12.29%)	13 (17.33%)	344 (11.19%)
<b>Number with 1 or more hospitalizations (past 3 years)</b>	1,421 (22.86%)	294 (22.46%)	421 (23.96%)	19 (25.33%)	687 (22.34%)
<b>Emergency visits (past 3 years)</b>					
Median (IQR)	2.0 (0.0-4.0)	2.0 (0.0-4.0)	1.0 (0.0-4.0)	1.0 (0.0-3.0)	2.0 (0.0-5.0)
0	1,762 (28.35%)	400 (30.56%)	553 (31.47%)	29 (38.67%)	780 (25.37%)
1	1,143 (18.39%)	233 (17.80%)	357 (20.32%)	13 (17.33%)	540 (17.56%)
2 to 4	1,789 (28.78%)	376 (28.72%)	500 (28.46%)	19 (25.33%)	894 (29.07%)
5+	1,522 (24.49%)	300 (22.92%)	347 (19.75%)	14 (18.67%)	861 (28.00%)
<b>Physician office visits (past 1 year)</b>					
Median (IQR)	21.0 (9.0-50.0)	15.0 (8.0-36.0)	14.0 (7.0-26.0)	11.0 (6.0-21.0)	33.0 (14.0-59.0)
0	61 (0.98%)	19 (1.45%)	20 (1.14%)	0 (0.00%)	22 (0.72%)
1 to 3	385 (6.19%)	109 (8.33%)	143 (8.14%)	7 (9.33%)	126 (4.10%)
4 to 6	546 (8.78%)	144 (11.00%)	214 (12.18%)	12 (16.00%)	176 (5.72%)
7 to 9	563 (9.06%)	148 (11.31%)	222 (12.64%)	10 (13.33%)	183 (5.95%)
10+	4,661 (74.98%)	889 (67.91%)	1,158 (65.91%)	46 (61.33%)	2,568 (83.51%)

	Overall	Oral	Topical	Transdermal	Injectable
<b>Specialist visits (past 1 year)</b>					
Cardiologist	1,711 (27.53%)	380 (29.03%)	530 (30.17%)	27 (36.00%)	774 (25.17%)
Endocrinologist	835 (13.43%)	121 (9.24%)	371 (21.12%)	13 (17.33%)	330 (10.73%)
Urologist	770 (12.39%)	176 (13.45%)	333 (18.95%)	11 (14.67%)	250 (8.13%)
<b>Charlson Morbidity Index</b>					
No hospitalization	4,795 (77.14%)	1,015 (77.54%)	1,336 (76.04%)	56 (74.67%)	2,388 (77.66%)
0	731 (11.76%)	146 (11.15%)	184 (10.47%)	6 (8.00%)	395 (12.85%)
1	*	67 (5.12%)	89 (5.07%)	≤5	123 (4.00%)
2	*	37 (2.83%)	62 (3.53%)	≤5	76 (2.47%)
3+	*	44 (3.36%)	86 (4.89%)	≤5	93 (3.02%)
<b>Co-morbidities</b>					
<b>Hypogonadism (past 3 years)</b>					
Physician visit with testicular dysfunction indicated	*	63 (4.81%)	183 (10.42%)	≤5	252 (8.20%)
Physician visit with testicular dysfunction or pituitary gland disorders indicated	804 (12.93%)	98 (7.49%)	302 (17.19%)	6 (8.00%)	398 (12.94%)
<b>HIV prior to cohort entry</b>	*	40 (3.06%)	238 (13.55%)	≤5	152 (4.94%)
<b>Diabetes prior to cohort entry</b>	1,428 (22.97%)	369 (28.19%)	525 (29.88%)	22 (29.33%)	512 (16.65%)
<b>Cardiovascular diseases and procedures (past 3 years)</b>					
Angina	*	43 (3.28%)	63 (3.59%)	≤5	79 (2.57%)
AMI	*	16 (1.22%)	23 (1.31%)	≤5	32 (1.04%)
Atrial fibrillation and flutter	52 (0.84%)	13 (0.99%)	16 (0.91%)	0 (0.00%)	23 (0.75%)
CHF	*	9 (0.69%)	17 (0.97%)	≤5	23 (0.75%)
Coronary artery bypass surgery	*	≤5	7 (0.40%)	0 (0.00%)	9 (0.29%)
Hypertension	2,026 (32.59%)	490 (37.43%)	681 (38.76%)	24 (32.00%)	831 (27.02%)
Percutaneous coronary intervention	*	19 (1.45%)	29 (1.65%)	≤5	24 (0.78%)
Peripheral vascular disease	16 (0.26%)	≤5	≤5	0 (0.00%)	6 (0.20%)
Stroke/TIA	*	9 (0.69%)	9 (0.51%)	≤5	17 (0.55%)
Ventricular dysrhythmia	*	22 (1.68%)	24 (1.37%)	≤5	39 (1.27%)
<b>Any cardiovascular disease or procedure (past 3 years)</b>	2,103 (33.83%)	506 (38.66%)	708 (40.30%)	27 (36.00%)	862 (28.03%)

*\*In accordance with the ICES privacy policy, in cases where the number of total users is less than 6, this number has been suppressed to ensure confidentiality. In cases where there is only one record being suppressed, another record has been suppressed as well in order to avoid residual disclosure issues.*

6,216 males under 65 were treated with provincially-funded testosterone products in Ontario in 2012. These patients tended to use injectable formulations, live in urban areas, and have lower socioeconomic status. Comorbidities differed between males using different testosterone formulations.

### Summary of Findings for Exhibit 17

1. 6,216 males younger than 65 in Ontario were treated with provincially-funded testosterone products in 2012.
2. The majority of treated testosterone patients were using injectable testosterone (N=3,075, 49.5%), lived in urban areas (N=5,484, 88.1%), were not living in long term care facilities (99.7%) and had lower socioeconomic status.
3. Injectable testosterone users were more likely to have ten or more physician office visits within the last year (83.5%) and five or more emergency department visits within the last three years (28.0%) compared to oral (67.9% and 22.9%, respectively), topical (65.9% and 19.8%, respectively), and transdermal patch (61.3% and 18.7%, respectively) testosterone users.
4. Cardiologists were the most commonly visited specialist within the last year (N=1,711, 27.5%) followed by endocrinologists (N=835, 13.4%) and urologists (N=770, 12.4%).
5. Between  $\leq 8.1\%$  (N=503) and 12.9% (N=804) of testosterone users had a documented diagnosis of hypogonadism according to claims data, defined as a physician visit with a testicular dysfunction indicated or a physician visit with either a testicular dysfunction or pituitary gland disorder indicated, respectively. A diagnosis of hypogonadism was lowest among transdermal patch users (between  $\leq 0.1\%$  and 8.0%) and highest among topical testosterone users (between 10.4% and 17.2%).
6. The number of testosterone users with diabetes and hypertension was lower among injectable testosterone users (16.7% and 27.0%, respectively) compared to the other groups (29.2% and 38.0%, respectively).
7. Topical testosterone users had more diagnosis of HIV (13.6%) compared to other testosterone groups ( $\leq 4.4\%$ ).

**Exhibit 18: Baseline characteristics of provincially-funded testosterone users 65 and older in Ontario by formulation, calendar year 2012**

	Overall	Oral	Topical	Transdermal	Injectable
<b>Number of users</b>	<b>8,460</b>	<b>2,666</b>	<b>3,665</b>	<b>86</b>	<b>2,043</b>
<b>Age</b>					
Median (IQR)	71.3 (67.8-76.4)	72.0 (68.1-77.4)	70.8 (67.5-75.4)	71.5 (68.5-75.9)	71.6 (67.8-77.2)
65-74	5,825 (68.85%)	1,750 (65.64%)	2,665 (72.71%)	59 (68.60%)	1,351 (66.13%)
75-84	2,259 (26.70%)	765 (28.69%)	888 (24.23%)	22 (25.58%)	584 (28.59%)
85-100	*	151 (5.66%)	112 (3.06%)	≤5	108 (5.29%)
<b>Urban residence</b>	7,237 (85.54%)	2,229 (83.61%)	3,179 (86.74%)	62 (72.09%)	1,767 (86.49%)
<b>LTC Resident</b>	28 (0.33%)	11 (0.41%)	7 (0.19%)	0 (0.00%)	10 (0.49%)
<b>Socioeconomic status</b>					
Q1 (lowest)	1,287 (15.21%)	427 (16.02%)	506 (13.81%)	12 (13.95%)	342 (16.74%)
Q2	1,543 (18.24%)	517 (19.39%)	597 (16.29%)	15 (17.44%)	414 (20.26%)
Q3	1,562 (18.46%)	488 (18.30%)	662 (18.06%)	22 (25.58%)	390 (19.09%)
Q4	1,800 (21.28%)	582 (21.83%)	820 (22.37%)	12 (13.95%)	386 (18.89%)
Q5 (highest)	2,240 (26.48%)	647 (24.27%)	1,068 (29.14%)	24 (27.91%)	501 (24.52%)
<b>Number with 1 or more hospitalizations (past 3 years)</b>	2,446 (28.91%)	747 (28.02%)	1,025 (27.97%)	32 (37.21%)	642 (31.42%)
<b>Emergency visits (past 3 years)</b>					
Median (IQR)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	1.00 (0.0-2.0)
0	3,770 (44.56%)	1,209 (45.35%)	1,666 (45.46%)	30 (34.88%)	865 (42.34%)
1	1,807 (21.36%)	553 (20.74%)	795 (21.69%)	23 (26.74%)	436 (21.34%)
2 to 4	2,035 (24.05%)	645 (24.19%)	851 (23.22%)	22 (25.58%)	517 (25.31%)
5+	848 (10.02%)	259 (9.71%)	353 (9.63%)	11 (12.79%)	225 (11.01%)
<b>Physician office visits (past 1 years)</b>					
Median (IQR)	11.0 (6.0-17.0)	9.0 (5.0-15.0)	10.0 (6.0-16.0)	9.0 (6.0-17.0)	14.0 (8.0-22.0)
0	57 (0.67%)	23 (0.86%)	25 (0.68%)	0 (0.00%)	9 (0.44%)
1 to 3	772 (9.13%)	322 (12.08%)	308 (8.40%)	9 (10.47%)	133 (6.51%)
4 to 6	1,428 (16.88%)	506 (18.98%)	699 (19.07%)	13 (15.12%)	210 (10.28%)
7 to 9	1,465 (17.32%)	518 (19.43%)	677 (18.47%)	22 (25.58%)	248 (12.14%)
10+	4,738 (56.00%)	1,297 (48.65%)	1,956 (53.37%)	42 (48.84%)	1,443 (70.63%)
<b>Specialist visits (past 1 year)</b>					
Cardiologist	3,647 (43.11%)	1,111 (41.67%)	1,602 (43.71%)	33 (38.37%)	901 (44.10%)
Endocrinologist	1,217 (14.39%)	230 (8.63%)	628 (17.14%)	11 (12.79%)	348 (17.03%)
Urologist	2,514 (29.72%)	681 (25.54%)	1,284 (35.03%)	21 (24.42%)	528 (25.84%)

	Overall	Oral	Topical	Transdermal	Injectable
<b>Charlson Morbidity Index</b>					
No hospitalization	6,014 (71.09%)	1,919 (71.98%)	2,640 (72.03%)	54 (62.79%)	1,401 (68.58%)
0	1,132 (13.38%)	331 (12.42%)	500 (13.64%)	12 (13.95%)	289 (14.15%)
1	518 (6.12%)	166 (6.23%)	206 (5.62%)	≤5	*
2	394 (4.66%)	127 (4.76%)	156 (4.26%)	6 (6.98%)	105 (5.14%)
3+	402 (4.75%)	123 (4.61%)	163 (4.45%)	9 (10.47%)	107 (5.24%)
<b>Co-morbidities</b>					
<b>Hypogonadism (past 3 years)</b>					
Physician visit with testicular dysfunction indicated	805 (9.52%)	141 (5.29%)	327 (8.92%)	8 (9.30%)	329 (16.10%)
Physician visit with testicular dysfunction or pituitary gland disorders indicated	1,230 (14.54%)	200 (7.50%)	534 (14.57%)	10 (11.63%)	486 (23.79%)
<b>HIV prior to cohort entry</b>	*	9 (0.34%)	34 (0.93%)	≤5	21 (1.03%)
<b>Diabetes prior to cohort entry</b>	3,142 (37.14%)	1,015 (38.07%)	1,332 (36.34%)	36 (41.86%)	759 (37.15%)
<b>Cardiovascular diseases and procedures (past 3 years)</b>					
Angina	669 (7.91%)	205 (7.69%)	269 (7.34%)	7 (8.14%)	188 (9.20%)
AMI	*	48 (1.80%)	60 (1.64%)	≤5	50 (2.45%)
Atrial fibrillation and flutter	378 (4.47%)	115 (4.31%)	165 (4.50%)	7 (8.14%)	91 (4.45%)
CHF	*	46 (1.73%)	55 (1.50%)	≤5	53 (2.59%)
Coronary artery bypass surgery	114 (1.35%)	32 (1.20%)	52 (1.42%)	0 (0.00%)	30 (1.47%)
Hypertension (prior to cohort entry)	6,218 (73.50%)	1,966 (73.74%)	2,673 (72.93%)	61 (70.93%)	1,518 (74.30%)
Percutaneous coronary intervention	*	60 (2.25%)	80 (2.18%)	≤5	53 (2.59%)
Peripheral vascular disease	38 (0.45%)	13 (0.49%)	11 (0.30%)	0 (0.00%)	14 (0.69%)
Stroke/TIA	*	23 (0.86%)	33 (0.90%)	≤5	26 (1.27%)
Ventricular dysrhythmia	461 (5.45%)	139 (5.21%)	202 (5.51%)	7 (8.14%)	113 (5.53%)
<b>Any cardiovascular disease or procedure (past 3 years)</b>	6,349 (75.05%)	2,001 (75.06%)	2,739 (74.73%)	63 (73.26%)	1,546 (75.67%)

*\*In accordance with the ICES privacy policy, in cases where the number of total users is less than 6, this number has been suppressed to ensure confidentiality. In cases where there is only one record being suppressed, another record has been suppressed as well in order to avoid residual disclosure issues.*

8,460 males aged 65 and older were treated with provincially-funded testosterone products in Ontario in 2012. These patients tended to use topical formulations, live in urban areas, and have higher socioeconomic status.

### Summary of Findings for Exhibit 18

1. 14,676 males were treated with provincially-funded testosterone products in Ontario in 2012, just over half of whom (N=8,460, 57.6%) were aged 65 years and older.
2. The majority of older (65+) testosterone users were using topical testosterone (N=3,665, 43.3%), lived in urban areas (N=7,237, 85.5%), were not living in long term care facilities (99.7%) and had higher socioeconomic status.
3. Older testosterone users had similar hospital utilization; however, injectable users were more likely to have ten or more physician office visits within the last year (70.6%) compared to oral (48.7%), topical (53.4%) and patch (48.8%) users.
4. Cardiologists were the most commonly visited specialist within the last year (N=3,647, 43.1%) followed by endocrinologists (N=1,217, 14.4%) and urologists (N=2,514, 29.7%).
5. Between 9.5% (N=805) and 14.5% (N=1,230) of testosterone users had a documented diagnosis of hypogonadism according to claims data, defined as a physician visit with a testicular dysfunction indicated or a physician visit with either a testicular dysfunction or pituitary gland disorder indicated, respectively. A diagnosis of hypogonadism was lowest among oral users (between 5.3% and 7.5%) and highest among injectable testosterone users (between 16.1% and 23.8%). This differed from the younger population, where a hypogonadism diagnosis was higher among topical testosterone users.
6. Unlike younger testosterone users, older users had similar comorbidities regardless of the formulation used. The majority (N=6,218, 73.5%) had a diagnosis of hypertension and 37.1% (N=3,142) had a past diagnosis of diabetes.

## Patterns of Testosterone therapy use and discontinuation

Exhibit 19: Time to discontinuation among new male users of testosterone therapy, aged 66 and older in Ontario, 2008-2013

Testosterone	Received Only 1 Prescription %	Median time to discontinuation*
<b>Testosterone Therapy</b>	20-30%	9-12 months
Oral	20-30%	12-15 months
Topical	20-30%	9-12 months
Transdermal	30-40%	3-6 months
Injectable	40-50%	9-12 months

\*Among those prescribed >1 prescription

In general, new users of testosterone aged 66 and older treated with transdermal patch testosterone products discontinue therapy faster compared to males using oral, injectable and topical formulations.

### Summary of Findings for Exhibit 19

1. Among new male testosterone users aged 66 and older in Ontario initiating therapy between April 2008 and March 2012, the majority initiated topical testosterone (40-50%) followed by oral (20-30%), injectable (20-30%) and transdermal patch (<10%) testosterone.
2. Almost half of males aged 66 and older, initiating injectable testosterone received only one prescription before discontinuing therapy. In comparison, more males initiating oral, topical and patch formulations went on to receive another prescription.
3. Among patients with more than one testosterone prescription, adherence to oral testosterone was higher compared to topical, injectable and transdermal patch testosterone ( $p < 0.001$ ).
4. Along with lower adherence, transdermal patch testosterone users were more likely to have two or more different testosterone formulations dispensed over their course of continuous use.
5. Less than 20% of testosterone users had a documented diagnosis of hypogonadism, using claims data. This diagnosis was highest among injectable users followed by transdermal patch, topical and oral users.
6. About one-third of new testosterone users had no lab test for testosterone levels in year prior to their first prescription for therapy. However, this ranged (between 25-40%) depending on testosterone formulation initiated, with topical and transdermal patch testosterone users more likely to have had past testosterone level lab tests compared to oral and injectable users.

## Key Findings

### Overall National and Provincial Trends in Testosterone Use

Prescriptions for testosterone products in Canada have increased by almost 40% over the past 4 years, from 99,854 prescriptions in the last quarter of 2009 to 137,318 prescriptions by the first quarter of 2014, the majority of which were for topical formulations (46%). By the beginning of 2014, Ontario had the fourth-highest rate of provincially-funded prescriptions for testosterone (508 prescriptions dispensed per 100,000 eligible population compared to the national average of 489 prescriptions dispensed per 100,000 eligible population) and highest costs of provincially-funded testosterone products (\$57,519 per 100,000 eligible population compared to the national average of \$44,192 per 100,000 eligible population). A decline in the number of prescriptions and costs was observed at the beginning of 2014. This may be due to cardiovascular concerns that prompted a re-evaluation of the drug class by Health Canada.

### National and Provincial Trends in Testosterone use among Public Drug Plan Beneficiaries

In 2012, Ontario had the highest provincial rate of testosterone use (1,105 users per 100,000 eligible men), overall cost (\$2 million) and highest average cost per user (\$137.5) among public drug plan beneficiaries, in Canada. This rate of use varied ten-fold across provinces, with the lowest rates observed in PEI and BC, which have more restrictive public plan listings. Injectable testosterone, which is listed as general benefit in most provinces, was the most utilized publically-funded testosterone across all provinces in Canada, except Ontario where topical testosterone use was highest. The low rates of topical testosterone utilization in provinces other than Ontario may be driven by the products having no listing (BC, Alberta, Saskatchewan, Manitoba) or enforced restricted listing (New Brunswick, Nova Scotia, PEI) compared to the unenforced restricted listing in Ontario. In Canada, the overall average cost per user for topical testosterone (\$347.4) was substantially higher than injectable testosterone (\$74.3), which may be contributing to the high average cost per user in Ontario. In 2012, Ontario had the second highest rate of testosterone use among younger (less than 65 years) and older (aged 65 and older) male beneficiaries, behind Alberta and Manitoba, respectively. Among younger male public drug plan beneficiaries in 2012, Ontario has the highest rate of oral and topical testosterone use (233 and 300 users per 100,000 eligible men, respectively) and second highest (behind Alberta) rate of injectable testosterone use (508 users per 100,000 eligible men). Among older male public plan beneficiaries, Ontario had the highest rate of topical testosterone use (327 users per 100,000 eligible men), third highest (behind Saskatchewan and Nova Scotia) rate of oral use (241 users per 100,000 eligible men) and fifth highest rate of injectable use (157 users per 100,000 eligible men) in 2012. The transdermal patch received minimal use across provinces in Canada.

### Use of Testosterone Products in Ontario

Over half of testosterone prescriptions in Ontario are paid for through non-public drug coverage (65.3%). Among public drug plan beneficiaries in Ontario, testosterone use is lower among older (aged

65 and older) males compared to younger (less than 65 years) males (726 and 1,053 users per 100,000 eligible, respectively) by the end of 2012. Testosterone rates of use among older and younger beneficiaries have increased in Ontario, despite the introduction of universal prescribing restrictions in 2006. This is largely driven by the use of topical testosterone, which was added to the provincial formulary in 2005 and increased substantially among both younger (from 50 to 300 users per 100,000 eligible men) and older (from 11 users to 327 users per 100,000 eligible men) beneficiaries, between 2005 and 2012. By the end of 2012, topical testosterone was the most utilized publically-funded testosterone among older Ontario beneficiaries, which differed from the younger population where injectable testosterone had the highest rate of use. The rate of transdermal patch testosterone has remained negligible in Ontario among both age groups.

### **Characteristics of Testosterone users in Ontario**

In 2012, there were 6,216 younger and 8,460 older male users of provincially-funded testosterone products in Ontario. Among the younger users, the majority were using injectable testosterone, lived in urban areas, had low socioeconomic status, low comorbidities and had more than 10 physician visits within the last year. Injectable testosterone users had a higher rate of health care utilization, but lower rates of comorbidities such as hypertension and diabetes, compared to the other testosterone users. Among the older testosterone users, the majority were using topical testosterone, lived in urban areas, had high socioeconomic status, more comorbidities and had less health care utilization. Older users had similar comorbidities regardless of the type of formulation used. On average, less than 15% of testosterone users had a documented diagnosis of hypogonadism according to claims data, despite this being the main criterion for TRT reimbursement. HIV is also a criterion for reimbursement, but was present in less than 7% of young users and less than 1% of older male users.

### **Testosterone Patterns of Use in Ontario**

Between April 2008 and March 2013, almost half of all male beneficiaries aged 66 and older, that were new users of provincially-funded testosterone products in Ontario, were treated with topical testosterone. This was followed by oral testosterone, injectable testosterone and transdermal patch testosterone. Among new users, the majority had more than one prescription, however almost half of users initiating injectable testosterone had only one prescription. Among the patients who had more than one prescription for testosterone, adherence to therapy was highest among those prescribed oral testosterone, followed by topical testosterone, injectable testosterone and transdermal patch testosterone ( $p < 0.001$ ). A documented diagnosis of hypogonadism through claims data was low ( $< 20\%$ ) among new testosterone users, but differed across testosterone formulation users, with patients initiating injectable formulation being more likely to have a documented diagnosis. About one-third of new testosterone users did not receive a lab test for testosterone levels in year prior to their first prescription for therapy. Testosterone users had similar comorbidities across formulation groups. The majority of new testosterone users had a diagnosis of hypertension, almost half had a past diagnosis of diabetes and the majority did not have a diagnosis of HIV.

## Cyclic Trends

We observed a major cyclic trend in rates of provincially-funded use of TRT products in Manitoba, with rates being highest in the first quarter of the year and lowest in the second quarter of the year. Manitoba has an expanded public drug coverage among the younger population through their PharmaCare programs, and therefore it is likely that this phenomenon is being driven by patterns of deductible payments and associated stockpiling of drugs near the end of the coverage period (fiscal year [April – March]).

## Health Equity

Stratified analyses suggest that there isn't a major equity issue in access to these medications by age. Overall, testosterone utilization was only slightly higher among older patients, which may indicate overuse in this older population. Given the passive restricted listing of these products on the Ontario public drug formulary, rates of use of testosterone in the Ontario population eligible for drug coverage are among the highest in Canada suggesting no considerable access issues.

## Limitations

### Data Availability

Several limitations to availability of data warrant discussion:

1. No data is available for the Territories, and therefore all analyses are restricted to inter-provincial comparisons.
2. IMS Geographic Prescription Monitor (GPM<sup>12</sup>) does not collect patient-level data, and therefore information on privately funded prescriptions is only available at the prescription and unit (e.g. tablet) level.
3. There is no data available for publically paid prescriptions in Quebec and Newfoundland & Labrador from NPDUIS. Therefore, we will be unable to make comparisons between Ontario rates and rates of use in these provinces.
4. Data on the number of individuals eligible for public drug coverage was estimated based on prescription trends (where available) and public annual reports. Therefore, these may slightly underestimate the true size of the public beneficiary population; however, this does reflect the number of active beneficiaries (e.g. those filling at least one prescription over a given year) each year.
5. Diagnoses of HIV and congestive heart failure rely on administrative databases. Although these databases have been validated, and have high sensitivity and specificity, some misclassification of diagnoses is possible.
6. A diagnosis of hypogonadism is not well captured in administrative databases. Therefore the sensitivity and specificity are unknown. Some misclassification of diagnoses is possible. In

particular, some of the individuals treated with testosterone products with no indication of hypogonadism may in fact have minor disease that is not picked up in the administrative data.

7. Although we measured the number of testosterone lab tests among new testosterone users, the outcome of these lab tests are unknown. Therefore, we do not know if the value of the lab test meets criteria for testosterone treatment. The number of testosterone laboratory tests among new testosterone users may be underestimated as the code does not capture those patients that were tested in hospital laboratories.

### Generalizability

1. All analyses using IMS Geographic Prescription Monitor (GPM<sup>12</sup>) data reflect medication use among the entire population.
2. Analyses of prescribing trends conducted among public drug beneficiaries were restricted to those aged 15 and older, and therefore are only generalizable to this population.
3. Due to incomplete data on public drug plan eligibility in Ontario among those aged less than 65 years, we restricted our analysis of drug adherence among new users of testosterone products to patients aged 66 and older. Therefore, these findings may not be generalizable to the younger population of testosterone users.

### Adherence

All data used in these analyses are based on dispensing patterns, and therefore we do not know whether subjects actually took the medications. This is particularly questionable among the population of individuals who only received one prescription for a testosterone product. It is possible that they never tried the medication, or tried it and did not finish their initial course of therapy. For this reason, we looked at characteristics among testosterone users who were dispensed more than one prescription.

## Appendix A: Public Plan Listings for Testosterone Products in Canada, by Province

Drug	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB/ NU/ NW
<b>Oral</b>												
testosterone undecanoate	No	Res	Ben	Ben	Pas	Ben	Res	Ben	Res	Res	Ben	Ben
<b>Long-acting injectable</b>												
testosterone cypionate	Res	Ben	Ben	Ben	Pas	Ben	Ben	Ben	No	Ben	Ben	Ben
testosterone enanthate	Res	Ben	Ben	Ben	Pas	Ben	Ben	Ben	Ben	Ben	Res	Ben
<b>Topical</b>												
testosterone transdermal patch (Androderm)	No	Res	No	No	Pas	Ben	Res	Res	No	Res	Ben	No
testosterone 1% topical gel (Testim)	No	No	No	No	Pas	Ben	Res	Res	Res	Res	Ben	No
testosterone 1% gel foil packet (Androgel)	No	No	No	No	Pas	Ben	Res	Res	Res	Res	No	No
testosterone 2% topical solution (Axiron)	No											

No=not listed

Res=restricted listing – enforced

Pas= restricted listing – passive

Ben=unrestricted listing

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