

Testosterone Replacement Therapy

Environmental Scan and Local/Historical Context

December 1, 2014

Executive Summary

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

In Canada, testosterone is available as a long-acting injectable (testosterone cypionate and testosterone enanthate), oral product (testosterone undecanoate) or topical product [testosterone transdermal patch (Androderm), testosterone 1% topical gel (Testim), testosterone 1% gel foil packet and pump (AndroGel) and testosterone 2% axillary topical solution (Axiron)]. The long-acting injectable testosterone cypionate and oral testosterone are available as generic products. The cost of a one-month supply for the oral generic product is \$17-51, for the injectable products \$29-51 and for the topical products \$60-200.

In Ontario, commercially available testosterone products (including oral, long-acting injectable, AndroGel, Testim and Androderm) are listed as “limited use” products. Restriction criteria limit the use of these testosterone products for male patients with confirmed serum testosterone levels associated with documented and symptomatic hypothalamic, pituitary or testicular disease, or in HIV-infected patients. Across Canada, special authorization is required for selected topical products in 5 jurisdictions; five jurisdictions do not provide coverage for these products. Although restriction criteria vary among the public drug plans, most state that the testosterone products are indicated for treatment of congenital and acquired primary or secondary hypogonadism in males.

Part B: Guidelines for the management of patients with hypogonadism

Five consensus recommendations and/or guidelines were reviewed for the management of men with hypogonadism: Endocrine Society (2010), European Association of Urology (2012), British Society for Sexual Medicine (2010), International Society of Andrology/International Society for the Study of the Aging Male, European Association of Urology/European Academy of Andrology/American Society of Andrology (2009), Canadian panel (2010). There are no formal Canadian guidelines available for the management of hypogonadism.

All guidelines suggest that choice of testosterone formulation should be based on numerous factors including patient’s preference, treatment burden and cost, and should be made as a joint decision between patient and physician. Although four of the five guidelines/consensus recommendations suggest that diagnosis of hypogonadism should be based on consistent signs and symptoms as well as low serum testosterone levels, there is no consensus regarding the number of signs/symptoms that must be present before making a diagnosis, nor is there consensus regarding the definition of a low serum testosterone level.

Part C: Impact of different drug reimbursement schemes for testosterone replacement products

Despite these agents, in particular the topical products, being restricted through the use of prior authorization in both Canada and international jurisdictions, there is a paucity of literature assessing these reimbursement schemes for adherence or usage patterns. One study showed that a restriction policy (using Limited Use codes) in Ontario resulted in a temporary decrease in testosterone prescribing;

however, testosterone use rose over 450% in the six years after implementation of the restriction policy suggesting that such a policy has minimal long-term effect testosterone use.

Part D: Rapid Review of Selected Topics

Choice of treatment for testosterone replacement therapies: In Canada, testosterone is available as an oral formulation, as an intramuscular injectable agent and in various topical preparations including gels, patch and topical axillary solution. Selection of a product is based on the patient's preference, pharmacokinetics of the testosterone formulation, treatment burden, cost and safety profile.

Adherence to testosterone replacement therapies: Information on adherence and/or persistence with testosterone replacement therapy has been inconsistent, with some studies showing poor adherence (i.e., 15% by 12 months) and other showing high adherence patterns (e.g., 91% after 12 months). In one study, TRT was used in a cyclic fashion (i.e., patients used TRT for a few months, stopped treatment for 2-3 months and then restarted TRT with the same dose and medication.)

Testosterone levels: Controversy still exists regarding reference ranges for normal levels of testosterone. Most guidelines suggest that total testosterone level above 12 nmol/L does not require replacement; patients with serum levels below 8nmol/L will usually benefit from treatment. As well, it is recommended that testosterone levels be measured prior to commencement of treatment.

Table of Contents

List of Exhibits	6
Acknowledgments.....	7
Introduction	8
Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally.....	10
Availability and Costs of Testosterone Replacement Therapy (TRT) in Canada	10
Common Drug Review	12
TRT product listing in Ontario	12
Public Plan Listings in Canada	13
Restriction Criteria	14
Selected International Jurisdictions.....	16
Part B: Guidelines for the management of men with hypogonadism	21
Part C: Impact of different drug reimbursement schemes for testosterone replacement therapies	23
Methods.....	23
Results.....	23
Part D: Rapid Review of Selected Topics.....	24
Choice of Treatment for Testosterone Replacement Therapy	24
Adherence to Testosterone Products	25
Testosterone Levels	26
Health Canada and Food and Drug Administration (FDA) Alerts and Warnings	27
Discussion.....	27
Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally.....	27
Availability in Canada	27
Public Plan Listing in Ontario	28
Public Plan Listing in Canada.....	28
Selected International Jurisdictions.....	28
Part B: Guidelines for the management of patients with hypogonadism	28
Part C: Impact of different drug reimbursement schemes for testosterone replacement therapy.....	29

Part D: Rapid Reviews of Selected Topics	29
Health Equity.....	29
Conclusion.....	29
Reference List.....	31
Appendix 1: Restriction Criteria for Testosterone Products in Canada	35
Appendix 2: Webpages for Provincial Drug Formularies	37
Appendix 3: Interview Questions.....	38
Appendix 4: Tiered cost-sharing options	39

List of Exhibits

Exhibit 1: Testosterone replacement therapy available in Canada	11
Exhibit 2: Public plan listings in Canada for testosterone products	14
Exhibit 3: Summary of Provincial Criteria for Testosterone Products	14
Exhibit 4: Summary of interviews with representative from public drug program	15
Exhibit 5: Listing of testosterone products for select plans in the United States*	17
Exhibit 6: Testosterone Replacement Therapies (Australia).....	19
Exhibit 7: TRT products (Scotland)	20
Exhibit 8: Comparison of guidelines for management of men with hypogonadism	21
Exhibit 9: Choice of Treatment for Testosterone Replacement Therapy	25

Acknowledgments

This review was funded by grants from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Health System Research Fund and Drug Innovation Fund. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES, CIHI, or the Ontario MOHLTC is intended or should be inferred.

A special thank you to all of the provincial and territorial representatives in Canada from the respective Ministries of Health as well as the representative from the Non-Insured Health Benefits for First Nations and Inuit (NIHB) who participated in the telephone survey.

Introduction

Testosterone replacement therapy (TRT) has been available since the 1950's in Canada for the treatment of hypogonadism. Hypogonadism results from testicular failure (e.g., Klinefelter syndrome, testicular tumors)(referred to as primary hypogonadism), or is due to hypothalamic-pituitary dysfunction (e.g., hyperprolactinemia, Kallmann syndrome)(referred to as secondary hypogonadism), or both (e.g., late-onset hypogonadism).¹⁻³ Medications can also result in hypogonadism, in particular glucocorticoids in supraphysiological doses and opioid analgesics.³ Testosterone level increases until the age of 17 years, when it stabilizes until the ages of 35-40 years; thereafter, levels decline at 1.2-2% per year. Approximately 20% of men over the age of 60 years and about 50% of men older than 80 years have serum testosterone levels that are subnormal compared with younger men.¹

Clinical symptoms vary with age of onset, duration and severity of the deficiency. In infants and pubertal males, hypogonadism is often recognized due to an anatomic abnormality (e.g., failure of testicular descent) or delayed or absent testicular growth or puberty. In late-onset hypogonadism, symptoms such as decreased muscle mass, loss of libido and impotence, and poor concentration and decreased energy may be mistaken for signs of aging.¹

Although the use of TRT for the treatment of primary and secondary hypogonadism (“classical hypogonadism”) is considered standard of care, controversy still exists regarding treatment of aging men with testosterone.⁴ Different terms have been used to describe hypogonadism in the aging male including androgen deficiency syndrome, andropause, age-related androgen deficiency, male menopause, late-onset hypogonadism, androgen deficiency in the aging male (ADAM).⁵ Male hypogonadism may increase the risk for cardiovascular disease, type 2 diabetes mellitus, metabolic syndrome and Alzheimer's disease.^{1,2}

Primary hypogonadism is uncommon. Klinefelter syndrome, the most frequent form of primary hypogonadism, affects approximately 0.2% (about 1 in 600 live births) of the male population.³ Testicular tumors occur in about 12 per 100,000 males; approximately 25% of patients have testosterone deficiency after treatment.² Forms of secondary hypogonadism include Kallmann syndrome (prevalence 1 in 10,000), Prader-Willi syndrome (prevalence 1 in 10,000), congenital adrenal hypoplasia with hypogonadotropic hypogonadism (prevalence 1 in 12,500 individuals), hyperprolactinemia (caused by prolactin-secreting pituitary adenomas or drug-induced), non-functioning pituitary adenomas and post-pituitary surgery.² The prevalence of unequivocal hypogonadism (testosterone less than 6 nmol/L) is reported as 6.3% in a survey conducted in the UK.⁶

The prevalence of late-onset hypogonadism is not well defined, and has varied from 2 to 40%⁷⁻⁹, depending on various factors including the population studied and the definition of hypogonadism. In one study, the overall prevalence of late-onset hypogonadism was 2.1%. For men aged 40 to 49 years of age, the prevalence was 0.1%, and increased to 5.1% for those 70 to 79 years of age.⁸ Prevalence is higher among those with specific comorbidities, including HIV, diabetes mellitus and obesity.³

The diagnosis of late-onset hypogonadism is not consistent among the various guidelines or consensus recommendations. In the aging male, there is on average a 1-2% decline of total testosterone per year

with a more rapid decline in free testosterone levels.¹⁰ The authors of one study suggest requirement of the presence of at least three sexual symptoms with a total testosterone level of less than 11 nmol/L and a free testosterone level of less than 220 pmol/L.⁸ Guidelines from the European Association of Urology² and the Endocrine Society¹¹ recommend a diagnosis of hypogonadism based on persistent signs and symptoms and consistently low testosterone levels, measured on more than one occasion. It should be noted that not all men with low testosterone levels are symptomatic.^{7,9} For example, in one study, presence of one or more symptoms occurred in 66% of patients with testosterone levels less than 300 ng/dL (<10.1 nmol/L).⁷ Another study showed that 37-47% of subjects with total testosterone levels less than 200 ng/dL (<6.9 nmol/L) failed to have three or more symptoms.⁹

Testosterone replacement therapy is used in men with a confirmed diagnosis of hypogonadism. TRT is used to establish and maintain secondary sexual characteristics, sexual function, body composition and quality of life.³ The target testosterone concentration is individualized, but the goal is to achieve levels in the mid-normal range. Various testosterone products and formulations are available in Canada. All testosterone products, regardless of formulation, are federally designated controlled substances. Under Ontario's Narcotics Safety and Awareness Act 2010, the Ministry of Health Long-Term Care requires the collection and disclosure of personal health information to monitor prescribing, dispensing and to ensure the appropriate use of testosterone and other controlled substances.¹² Intramuscular testosterone esters (testosterone enanthate and cypionate) are long-acting preparations that are administered every 2-3 weeks, with peak concentrations occurring shortly after injection and gradual decline after 7-15 days.¹ Oral testosterone (testosterone undecanoate) requires multiple, high daily doses due to low bioavailability.¹ There are four topical/transdermal testosterone products available in Canada that are applied once daily: testosterone transdermal patch (Androderm), testosterone 1% topical gel (Testim), testosterone 1% gel foil packet (Androgel) and testosterone 2% topical solution (Axiron).

The objectives of this report are:

- Part A: To summarize coverage of testosterone replacement therapy through public drug programs in Ontario and across Canada, as well as in select international jurisdictions
- Part B: To summarize the guidelines for management of patients with hypogonadism
- Part C: To review the evidence relating to the impact of different drug reimbursement schemes for testosterone replacement therapy (e.g. cost sharing options) on patient access and/or utilization and costs
- Part D: To provide rapid reviews on selected topics, including choice of treatment for testosterone replacement therapy and adherence to testosterone therapy

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability and Costs of Testosterone Replacement Therapy (TRT) in Canada

In Canada, testosterone is available as a long-acting injectable, oral product or topical product. There are two long-acting testosterone injectable products: testosterone cypionate and testosterone enanthate. Only one product is available as an oral product: testosterone undecanoate. Four topical products are commercially available: testosterone transdermal patch (Androderm), testosterone 1% topical gel (Testim), testosterone 1% gel foil packet (Androgel) and testosterone 2% topical solution (Axiron). The long-acting injectable products (testosterone cypionate and testosterone enanthate) and the oral testosterone (testosterone undecanoate) are available as generic products. Exhibit 1 outlines the dosage forms and costs (based on wholesale costs) for TRT products.

Exhibit 1: Testosterone replacement therapy available in Canada

Drug Name	Brand name	Manufacturer	Availability	DIN #	Recommended dose	Monthly cost*	Date available
Oral							
Testosterone undecanoate	Andriol	Merck	40mg capsule	00782327	Maintenance: 40-120mg/day (divided doses)	28.2-84.60 [†]	Dec 1992
	PMS-Testosterone	PMS	40mg capsule	02322498	Maintenance: 40-120mg/day (divided doses)	16.92-50.76 [†]	Oct 2009
Long-acting injectable							
Testosterone cypionate	Depo-Testosterone	Pfizer	100mg/mL (x10mL)	00030783	200 mg every 2 weeks	28.59 [†]	Dec 1953
	Testosterone Cypionate Injection USP	Sandoz	100mg/mL	02246063	200 mg every 2 weeks	23.58	Aug 2002
Testosterone enanthate	Delatestryl	Valeant	200mg/mL (x5mL)	00029246	100-400 mg every 4 weeks	50.57 [†]	Dec 1955
Topical							
Testosterone	Androderm	Watson	12.2mg/patch (2.5mg/day) 24.3mg/patch (5mg/day)	02239653 02245972	2.5-7.5mg/day (usual dose 5mg/day)	62.79-188.35 [†]	Dec 2000
Testosterone	Androgel	Abbott	2.5g/packet (1%)	02245346	5-10g/day	66.90-118.30 [†]	May 2002
			5g/packet (1%)	02249499			Sep 2004
			1.25g/actuation (pump)	02382369			
Testosterone	Axiron	Eli Lilly	30mg/actuation (metered dose pump-60 doses)	02382369	60mg once daily	141.35 ^{††}	May 2013
Testosterone	Testim	Auxilium	1% 5g tubes (unit dose) x 30	02280248	5-10g daily	108.09-216.18 [†]	April 2007

*Based on recommended dosages in product monographs

[†] Based on costs obtained from the Ontario Drug Benefit Formulary (Accessed: May 23, 2014)

^{††} Based on costs obtained from McKesson (Accessed: May 23, 2014)

Summary

- Testosterone is available as an oral formulation, long-acting injectable and topical products.
- The monthly cost ranges from \$23/month (for generic long-acting testosterone cypionate) to \$216/month (for highest dose of Testim).

Common Drug Review

The Common Drug Review (CDR) is a single process for reviewing new drugs and providing listing recommendations to participating publicly funded federal, provincial and territorial drug benefit plans in Canada; it was established in September 2003. None of the testosterone products (including the recently introduced topical products) underwent review through CDR.

TRT product listing in Ontario

Limited Use (LU)

Limited use (LU) drugs are drugs that have been deemed to have value in certain circumstances, although they may not be appropriate for general listing in the Formulary. Testosterone products (namely: Androgel, Testim, Androderm, Depo-Testosterone, Delatestryl and testosterone undecanoate capsules) are available as Limited Use products in Ontario since 2005. Prior to that date, they were available as general benefit on the ODB formulary.

The Limited Use criteria are as follows:

Code 397: For male patients with confirmed low morning serum testosterone levels associated with documented, symptomatic hypothalamic, pituitary or testicular disease, or in HIV-infected patients.

Note: Older males with nonspecific symptoms of fatigue, malaise, depression who have a low normal random testosterone level do not satisfy these criteria.

LU Authorization Period: 1 year.

Committee to Evaluate Drugs:

The Committee to Evaluate Drugs (CED) is the Ministry of Health and Long-term care's independent expert advisory committee on drug-related issues. In 2003-04, the CED reviewed and recommended Limited Use listing for oral testosterone, injectable testosterone, Androderm (12.2mg) and Androgel foil packets (but not the pump). Subsequently Testim was added as a limited use product in 2009.

The manufacturer of Axiron submitted a request for review to CED in 2013; the review is currently deferred until completion of the Drug Class Review.

Summary

- In Ontario, oral testosterone and injectable testosterone were available as general benefits until 2005. Thereafter, all listed testosterone products were available through the Limited Use program.

Public Plan Listings in Canada

Part 1: Listing Status

In order to determine the listing of testosterone products across Canada, the relevant webpages of the provincial drug formularies were searched (See Appendix 2). In Canada, all public plans provide coverage for at least one testosterone product for eligible patients. These products are available either as a general benefit or as a restricted benefit. The restricted benefit is enforced (e.g., prescriber is required to provide information, often in writing, regarding justification for use of testosterone products).

A summary of the various listings (see Exhibit 1) is as follows:

Long-acting injectable products

- General benefits without restrictions: Alberta, Saskatchewan, Manitoba, Quebec, New Brunswick, Nova Scotia, PEI (only testosterone enanthate), Newfoundland, Yukon, NIHB/NT/NU
- Restricted (enforced): British Columbia
- Restricted (passive): Ontario

Oral products

- General benefits without restrictions: Saskatchewan, Manitoba, Quebec, Nova Scotia, Yukon, NIHB/NU/NW
- Restricted (enforced): Alberta, New Brunswick, PEI, Newfoundland
- Restricted (passive): Ontario
- Not listed: British Columbia

Topical products

Androderm

- General benefits without restrictions: Quebec
- Restricted (enforced): Alberta, New Brunswick, Nova Scotia, Newfoundland
- Restricted (passive): Ontario
- Not listed: British Columbia, Saskatchewan, Manitoba, Prince Edward Island, NIHB/NU/NT, Yukon

Testim

- General benefits without restrictions: Quebec
- Restricted (enforced): PEI, New Brunswick, Nova Scotia, Newfoundland
- Restricted (passive): Ontario
- Not listed: British Columbia, Alberta, Saskatchewan, Manitoba, NIHB/NU/NT, Yukon

Androgel

- General benefits without restrictions: Quebec
- Restricted (enforced): PEI, New Brunswick, Nova Scotia, Newfoundland
- Restricted (passive): Ontario
- Not listed: British Columbia, Saskatchewan, Manitoba, Prince Edward Island, NIHB/NU/NT, Yukon

Axiron

- General benefits without restrictions: Quebec

- Not listed: all other jurisdictions in Canada

Exhibit 2: Public plan listings in Canada for testosterone products

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

No=not listed;

Res=restricted listing - enforced

Ben=unrestricted listing

Pas= restricting listing – passive

Restriction Criteria

In order for patients to be eligible for publically funded TRTs, various jurisdictions use restriction criteria (see Appendix 1). Summary of the restriction criteria is found in Exhibit 3.

Exhibit 3: Summary of Provincial Criteria for Testosterone Products

Criteria	AB	BC	ON	NB, PEI, NF	NS
Treatment of congenital and acquired primary or secondary hypogonadism in males	√			√	√
Not considered for use for treatment of androgen decline in the aging male (ADAM)	√		√	√	
Hypogonadism or orchiectomy or undescended testes or Klinefelter's syndrome or female-to-male transformation or pituitary tumour or removal of pituitary gland		√		√	√
Surgery of pituitary gland and low testosterone levels		√		√	√
AIDS-wasting syndrome and low testosterone levels		√	√		
Confirmed low morning serum testosterone levels associated with documented, symptomatic hypothalamic, pituitary or testicular disease			√		
Clinical features and confirmed by two separate free testosterone measurements				√	√

Part 2: Telephone Interview with Public Drug Program Representatives

A representative from each public drug program (except Quebec) was contacted to participate in a 30 minute telephone interview to gather further information about formulary listing of testosterone replacement therapies (see Appendix 3 for interview questions). Exhibit 4 summarizes the information obtained in the interviews.

Exhibit 4: Summary of interviews with representative from public drug program

Province	Listing	Was there ever a change in listing?	What was the basis for listing/change in listing?
British Columbia	Restricted (injectable); not listed (oral, topicals)	No	Topicals were reviewed in 2002/2003; at that time a decision was made not to fund based on cost of products
Saskatchewan	General benefit (oral, injectable); no listing (topicals)	No	Internal review in 2002 of topical products determined that no significant benefit over incremental cost.
Manitoba	General benefit (oral, injectable); no listing (topicals)	No	Topical products are not listed in the formulary, due to pricing concerns.
Ontario	Limited Use	Oral and injectable testosterone were available as general benefits prior to 2005	Review of testosterone replacement in 2003/04, with changes to listing in 2005, based on clinical knowledge, efficacy, safety and cost-effectiveness
New Brunswick PEI Newfoundland	Restricted (enforced) (oral, topical), general listing (injectable)	Topical testosterone products, including Androgel, Testim and Androderm (not added in PEI), were added to the formulary as special authorization products in 2008. Andriol was added in 2009.	Atlantic Common Drug Review (2008)
Nova Scotia	Restricted (enforced) (topical), general listing (oral, injectable)		
NIHB	Oral, injectable (general benefit); no listing for topicals	No recent change in listing status	Topical testosterone products can be accessed on a case-by-case basis
Yukon	Injectable oral, topicals (general benefit)	Topical products (Androderm and Testim) will be removed from the formulary in August 2014	An environmental scan showed that testosterone topical products were either not listed or listed as restricted products in other Canadian jurisdictions

NA: not applicable

Summary

- Oral product: Six of the 12 (50%) public drug programs in Canada list oral testosterone undecanoate as a general benefit. In five jurisdictions, the oral product is available on a restricted basis, requiring special authorization. In Ontario it is listed as a Limited Use Product. One province (BC) does not list this product.
- Long-acting injectable: These products are available as a general benefit in 10 jurisdictions (83%) and restricted in two. In Ontario, these products are listed as Limited Use Products
- Topical products: No topical treatment is listed on the formulary of five (42%) jurisdictions. It is a restricted listing (enforced or passive) in six (50%), and a general benefit in one jurisdiction. Topical testosterone products are listed as Limited Use products in Ontario.
- Although restriction criteria vary among the public drug plans, most state that the testosterone products are indicated for treatment of congenital and acquired primary or secondary hypogonadism in males. Five jurisdictions state that these products are not considered for use in the treatment of androgen decline in the aging male.

Selected International Jurisdictions

United States

As a measure to control ever-increasing costs associated with healthcare, the use of a preferred drug list (“formulary”) has been implemented in some jurisdictions. For example a preferred drug list is a list of medications that the provider will cover the cost for without the need to request a prior authorization. The preferred drugs are usually medications that are available generically or are the result of price negotiations between the pharmaceutical company and the provider. For example, in Oregon (Medicaid), the preferred topical testosterone product is Androgel (requiring prior authorization); Testim, Androderm and Axiron are considered non-preferred.

A tiered co-payment system is a combination of cost-sharing and a preferred drug list.¹³ Three-tier structures commonly assign generic medications the lowest copay, formulary brand medications a somewhat higher copay, and non-formulary brand medications the highest copay. Three-tier copays provide consumers with more choice than in a closed formulary (where tier three drugs would not be covered at all) and attempt to reduce the number of prior authorizations that are needed for drug approval.¹⁴ In a five-tier system, tier 1 includes preferred generic drugs, tier 2 non-preferred generic drugs, tier 3 preferred brand drugs, tier 4 non-preferred brand drugs and tier 5 specialty drugs (e.g., injectables) (see Appendix 4 for examples of copayments with tiered formulary systems). See Exhibit 5 for some sample listings of testosterone replacement therapies in the United States. Note: testosterone undecanoate (oral) is not commercially available in the United States.

Exhibit 5: Listing of testosterone products for select plans in the United States*

Drug Plan	Testim	Androderm	Androgel	Axiron	Injectable products
AETNA Preferred List (Chronic Medications: Asthma) (3-Tier system) (www.aetna.com)	Preferred	Non-preferred	Preferred	Non-preferred	Not listed
Amerigroup Medication Formulary (Medicaid markets in Florida, Louisiana, Maryland, Nevada, New Jersey and Washington) (www.providers.amerigroup.com)	Non-preferred	Preferred (prior authorization required)	Preferred (prior authorization required)	Non-preferred	Non-preferred
Blue Cross Blue Shield of South Carolina Preferred Drug List (www.southcarolinablues.com)	Tier 3 (non-preferred)	Tier 2 (preferred)	Tier 3 (non-preferred)	Tier 2 (preferred)	Tier 3 (non-preferred)
Blue Cross Blue Shield of Texas Standard Preferred Drug List (January 2014) (www.bcbstx.com)	Non-preferred	Preferred	Non-preferred	Non-preferred	Not listed
Connecticut Medicaid Preferred Drug List (www.ctdssmap.com)	Preferred	Non-preferred	Preferred	Non-preferred	Non-preferred
Idaho Medicaid Preferred Drug List (www.healthandwelfare.idaho.gov)	Preferred	Non-preferred	Preferred	Non-preferred	Not listed
Illinois Medicaid Preferred Drug List http://www2.illinois.gov/hfs/sitecollectiondocuments/pdl.pdf	Prior authorization required	Prior authorization required	Prior authorization required	Prior authorization required	Prior authorization required
Kaiser Permanente 2014 Medicare Part D Comprehensive Formulary (5-tier system) (www.healthy.kaiserpermanente.org)	Tier 4	Tier 3	Tier 4	Tier 4	Tier 2
Kentucky Preferred Drug List 2014 (www.kentucky.magellanmedicaid.com)	Non-preferred	Preferred	Preferred	Non-preferred	Not listed
Oregon Fee-for-Service Enforceable Physical Health Preferred Drug List 2014 (http://www.oregon.gov/oha/healthplan/pages/tools_prov/pdl.aspx)	Non-preferred	Non-preferred	Preferred (prior authorization)	Non-preferred	Preferred
Texas Medicaid Preferred Drug List (http://www.txvendordrug.com/pdl/)	Non-preferred (prior authorization required)	Non-preferred (prior authorization required)	Preferred	Non-preferred	Not listed

WellCare Comprehensive Formulary (Medicare Advantage Plans) (covers New York, Connecticut, Florida, Georgia, Hawaii and others) (5-tier system) (https://www.wellcare.com/medicare_formulary/new_york)	Tier 3	Nonformulary	Nonformulary	Nonformulary	Tier 3
Wellmark Prior authorization/Step therapy (http://www.wellmark.com/HealthAndWellness/DrugInformation/PharmacyHome.aspx)	Tier 4	Tier 4	Tier 2	Tier 4	Tier 1

*NOTE: Oral testosterone undecanoate is not available in the United States

Prior Authorization

Testim Transdermal (Tier 3) https://www.wellcare.com/medicare_formulary/new_york)

Covered Use: All FDA-approved indications not otherwise excluded from Part D.

Exclusion Criteria: Pregnancy Category X

Required Medical Information: Statement indicating diagnosis of hypogonadism in men with pretreatment total testosterone level below normal physiological value of 300 ng/dl or below normal reference level provided by the laboratory required.

Other Countries

Australia:

In Australia, the Pharmaceutical Benefits Scheme (PBS) restricts testosterone replacement therapies to specific populations.¹⁵ See Exhibit 6 for TRT products available under PBS.

A surveillance of testosterone prescribing in Australia was undertaken to compare use of these products between January 1992 to December 2010.¹⁶ Over the two decades, total annual expenditure increased ninefold, according to PBS data. However, despite the increase, there has been no change in the approved indications for use of testosterone or the frequency of these conditions. The authors suggest that the increase in use of testosterone products is driven by indications such as “andropause” and male sexual dysfunction.

Exhibit 6: Testosterone Replacement Therapies (Australia)

Product	Dosage form	Listing
Axiron	Testosterone 2% transdermal	Authority required: <ul style="list-style-type: none"> • 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 2 morning blood samples taken on different mornings. Androgen deficiency is confirmed by testosterone less than 8 nmol per L, or 8-15 nmol per 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
Androderm	Testosterone 2.5 mg/24 hr patch 5 mg/24 hr patch	
Testogel*	Testosterone 1% gel	
Testosterone implant*	100mg, 200mg implant	
Testosterone enanthate	250 mg/mL injection	
Testosterone undecanoate	40 mg capsule 1g/4mL injection*	

*Not available in Canada

New Zealand:

There are limited products listed on the New Zealand formulary as fully subsidized: testosterone transdermal patch 2.5 mg/24 hrs (Androderm), testosterone cypionate 100mg/mL, testosterone esters 250 mg/mL, testosterone undecanoate 40mg capsules and 250mg/mL injection.¹⁷ Note that no special authority is needed for these medications for eligible beneficiaries.

Scotland:

In Scotland, various testosterone products have been evaluated for use within NHS Scotland.¹⁸ See Exhibit 7 for advice for testosterone replacement products in Scotland.

Exhibit 7: TRT products (Scotland)

Product	Advice/criteria
Testosterone 2% gel (Tostran) (2007)	Replacement therapy with testosterone for male hypogonadism when testosterone deficiency has been confirmed by clinical symptoms and laboratory analyses. It is an alternative to other formulations of testosterone gel, with similar costs for equivalent doses. It is restricted to use as an alternative to testosterone patches for those patients requiring a transdermal delivery system. Testosterone gel is at least as effective as testosterone patches and costs less.
Testosterone 50mg/5g gel (Testim) (2006)	Replacement therapy for adult male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests. It is an alternative to another formulation of testosterone gel, of the same strength and cost, and is restricted to use as an alternative to testosterone gel patches for those patients requiring a transdermal delivery system. Testosterone is at least as effective as testosterone patches and costs less.
Testosterone gel (Testogel) (2003)	Replacement therapy for adult male hypogonadism is accepted for restricted use within NHS Scotland. It offers an alternative to testosterone patches for those patients requiring a transdermal delivery system. Testosterone gel is at least as effective as testosterone patches and costs less, so is a cost effective transdermal treatment for this condition
Testosterone undecanoate (Nebido) (2009)	As testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests. Compared with alternative intramuscular preparations it offers the advantage of reduced frequency of dosing with less inter-dose fluctuation of testosterone levels

Summary

- In the United States, many health plans restrict the use of testosterone products through a prior authorization process.
- In Australia, testosterone products (including topical, injectable, oral) are available through a Special Authorization process. In contrast, New Zealand funds testosterone patch (Androderm), testosterone injectable products and oral testosterone as a general listing.

Part B: Guidelines for the management of men with hypogonadism

Various consensus recommendations and guidelines are available for the management of men with hypogonadism. There are no formal Canadian guidelines available for the management of hypogonadism. A summary of these guidelines is below in Exhibit 8.

Exhibit 8: Comparison of guidelines for management of men with hypogonadism

	Endocrine Society ¹¹	ISA/ISSAM/ EAU/EAA/ASA ¹⁹	British Society for Sexual Medicine ²⁰	Canadian panel ²¹	European Association of Urology ²
Diagnosis					
Blood levels obtained in am between 7-11am	✓	✓	✓	✓	Not stated
Normal Testosterone levels	Use lower limit of normal established in laboratory (lower limit in some laboratories is 9.8-10.4 nmol/L)	No generally accepted lower limits of normal; however total testosterone level above 12 nmol/L does not require substitution, and levels below 8 nmol/L will usually benefit from treatment	Total testosterone level above 12 nmol/L does not require replacement; patients with serum levels below 8nmol/L will usually benefit from treatment	Not defined due to difficulties with equipment standardization and interlaboratory variability	Lower normal range (8-12 nmol/L)
Repeat testosterone levels	✓	Not explicitly stated	Abnormal (low or borderline) require confirmation with repeat T plus SHBG and LH, FSH and prolactin	Abnormal (low or borderline) require confirmation with repeat T plus SHBG and LH, FSH and prolactin	✓
Type of testosterone test recommended	Total testosterone level (free or bioavailable testosterone if total near lower limit of normal)	Total testosterone	Total testosterone	Bioavailable testosterone	Total testosterone (free testosterone if total close to lower normal range)
Based on consistent symptoms and signs and low serum testosterone levels	✓	✓	✓	Not explicitly stated	✓
Measurement of BMD in men with severe androgen deficiency or low trauma fracture	✓	Assessment of bone density at 2-yr intervals in hypogonadal men	Not stated	Not stated	Adult men with severe hypogonadism should be screened for concomitant osteoporosis

Screening					
Population recommended for screening	Sellar mass, treatment with medications that affect testosterone product/metabolism, HIV-associated weight loss, end-stage renal disease, moderate/severe COPD, infertility, osteoporosis or low trauma fracture, type 2 DM	Not stated	Not stated	Men with diabetes	Sellar mass, end-stage renal disease, treatment with medications that affect testosterone, moderate to severe COPD, osteoporosis or low trauma fractures, HIV infection with sarcopenia, type 2 DM, infertility, adult men with consistent and multiple signs and symptoms associated with late-onset hypogonadism
Treatment					
Choice of formulation	Based on patient's preference, consideration of pharmacokinetics, treatment burden and cost	Selection based on joint decision between patient and physician	Selection based on joint decision between patient and physician	Based on physician and patient discussions	Selection based on joint decision by patient and physician
Indications	Symptomatic men with classical androgen deficiency syndromes	Focus of recommendations was late-onset hypogonadism	Men with erectile dysfunction and/or diminished libido and documented testosterone deficiency	Focus of consensus was management of patients with testosterone deficiency syndrome (also known as andropause, or late-onset hypogonadism)	Delayed puberty (idiopathic, Kallmann syndrome) Klinefelter syndrome with hypogonadism Sexual dysfunction and low testosterone Low bone mass in hypogonadism Adult men with consistent and preferably multiple signs and symptoms of hypogonadism Hypopituitarism Testicular dysgenesis and hypogonadism

Summary

- Guidelines/consensus recommendations vary in the definition of normal testosterone levels. Three of the five reviews suggest that the lower normal range as 8-12 nmol/L (using total testosterone levels).
- Although four of the five guidelines/consensus recommendations suggest that diagnosis of hypogonadism is based on consistent symptoms and signs and low serum testosterone levels, there is no consensus regarding the number of signs/symptoms that must be present before making a diagnosis.
- All guidelines suggest that choice of testosterone formulation should be based on numerous factors including patient's preference, treatment burden and cost, and should be made as a joint decision between patient and physician.

Part C: Impact of different drug reimbursement schemes for testosterone replacement therapies

Methods

A literature search was conducted in Pubmed using the terms: testosterone AND (healthcare accessibility OR insurance coverage OR insurance pharmaceutical services OR health policy OR reimbursement incentive OR national health programs OR cost sharing). Bibliographies of identified articles were scanned for additional relevant articles.

Results

Despite testosterone replacement therapies being restricted in many jurisdictions, there is a lack of information in the literature detailing the impact of different drug reimbursement schemes. In one small retrospective study, 23 male HIV-1 infected patients who received at least one dose of IM testosterone were switched to topical therapy.²² Assessment of the clinical outcomes and estimated cost savings for patients switched were evaluated. After a median of 21.63 months (SD=12.9 months), 22 patients remained on topical testosterone and one patient returned to IM therapy after recurrence of symptoms. No adverse effects were reported in any of the patients. Utilization of the topically applied testosterone relative to the injectable formulations resulted in approximately \$81,000 fewer dollars spent (included drug acquisition cost, as well as cost of administration of IM testosterone).

In another recent time series analysis conducted in Ontario, a temporary decrease in testosterone prescribing was observed when a restriction policy (Limited Use code) was introduced in 2005 for all testosterone products, including the topical formulations.²³ Testosterone prescribing declined 27.9% in the 6 months following implementation of the restriction policy. However, by the end of the study period in 2010, the rate of testosterone use exceeded pre-policy levels; this increase was largely driven by the use of topical testosterone products which rose 464% between 2006 and 2012.

Summary

- There is a dearth of literature detailing the impact of different drug reimbursement options for testosterone replacement therapies.
- Data from Ontario have shown that a restriction policy (using Limited Use codes) may result in a temporary decrease in testosterone prescribing. However, testosterone use rose over 450% in the six years after implementation of the restriction policy suggesting that such a policy has minimal long-term effect on testosterone use.

Part D: Rapid Review of Selected Topics

Choice of Treatment for Testosterone Replacement Therapy

The objective of testosterone replacement therapy is to restore physiological testosterone levels in hypogonadal men.² Several products are available in Canada, and differ in their route of administration and pharmacokinetics. Selection of a product is based on the patient's preference, pharmacokinetics of the testosterone formulation, treatment burden, cost and adverse effects (see Exhibit 9).

Intramuscular testosterone esters (testosterone enanthate and cypionate) are long-acting preparations that are administered every 2-3 weeks, with peak concentrations occurring shortly after injection and gradual decline after 7-15 days. After IM injection of the testosterone ester, testosterone concentrations in serum rise into the supraphysiological range within 24-48 hours and gradually decline into the low-normal range over 2 weeks.³ However, resulting wide peak-to-trough fluctuations in serum testosterone levels may lead to instability in mood, libido and sexual function.^{1,2} As well, intramuscular testosterone may cause discomfort on injection. However, cost of the injection may be an important driver in the choice of an injectable product over a topical/transdermal preparation for some patients. For example, in one study cost was a statistically significant reason for a patient's preference for injectable therapy (34.5%) over gel (21.3%, $p=0.023$).²⁴

Oral testosterone is available as testosterone undecanoate. This product is absorbed into the systemic circulation through the lymphatic system and bypasses first-pass hepatic metabolism. In order to facilitate lymphatic absorption, oral testosterone undecanoate must be taken soon after meals.³ It is recommended that it be taken with at least 20 mg of fat.²⁵ It requires multiple, high daily doses due to low bioavailability; it often results in an irregular serum testosterone pattern during the course of the day.²⁵ As well, it can cause gastrointestinal upset; approximately 40% of patients report nausea and/or other GI complaints.^{1,26} In contrast to other oral forms of testosterone, such as methyltestosterone and fluoxymesterone, testosterone undecanoate does not appear to have appreciable hepatotoxicity.^{26,27} A 10-year safety study found that liver function test results were normal in 33 men receiving oral testosterone undecanoate 80-200mg.²⁸

Topical/transdermal preparations are available as skin patches, gel or underarm spray. They provide a uniform testosterone level for 24 hours (hence dosing once daily). Adverse effects include skin irritation at the site of application and possible risk of interpersonal transfer if appropriate precautions are not taken, in particular with the gel formulations.^{2,3} Accidental transference can lead to virilization of contacts, especially in children.²⁹ Although there are two gel preparations available (AndroGel and Testim), these products are not considered interchangeable. One report highlighted that patients who may not have responded to one gel preparation, may derive benefit from the alternative preparation.³⁰ In this study, 75/370 (20%) hypogonadal men on testosterone gel replacement therapy underwent a brand substitution, due to suboptimal clinical or biochemical response to initial product selection.

Exhibit 9: Choice of Treatment for Testosterone Replacement Therapy

Formulation	Route of administration	Interval for administration	Advantages	Disadvantages
Testosterone undecanoate	Oral	Twice daily	Absorbed through lymphatic system Convenient route of administration Flexible dosage and self-administered; immediate decrease in testosterone levels after interruption of treatment	Variable levels of testosterone Need for several doses per day with intake of fatty food
Testosterone cypionate, testosterone enanthate	Intramuscular	Every 2-3 weeks	Administered every 2-3 weeks (convenient); patients can self-inject	Discomfort on injection Possible fluctuation of testosterone levels Often administered by health care professional
Testosterone	Topical/transdermal	Once daily	Reliable steady-state testosterone levels Convenience of application	Skin irritation at site of application (patch: 19-66%, gel: 7-10%, axillary solution: 5-7%) ³ Risk of interpersonal transfer

Adapted from Dohle et al ²

Summary

In Canada, testosterone is available as an oral formulation, as an intramuscular injectable agent and in various topical preparations including gels, patch and topical axillary solution. Selection of a product is based on the patient's preference, pharmacokinetics of the testosterone formulation, treatment burden, cost and safety profile.

Adherence to Testosterone Products

Adherence is defined as the extent to which patients take medications as prescribed by their healthcare providers.³¹ Overall, lack of adherence has been linked to potentially negative clinical outcomes and higher costs.³² Adherence to topical testosterone replacement therapy (specifically AndroGel and Testim) was assessed using data from Thomas Reuters MarketScan database, containing record of commercially insured and Medicare-insured US patients.³¹ A total of 15,435 men with hypogonadism were included in the study. Overall, adherence to either AndroGel or Testim was low; only 35% of patients had continued on medication by 6 months, and by 12 months, only 15.4%. Patients with specific and nonspecific hypogonadal diagnosis had low adherence rates (32.7% vs. 29.4%, respectively). However, approximately 50% of men reinitiated therapy, usually on the same dose and dosage form; only 5% of men were switched to the other topical therapy. Another study used the same Truven MarketScan Database and same cohort of 15,435 men who received topical TRT prescription. An additional 517 men were identified who received short-lasting TRT injection. All men were followed for up to 30 months after treatment initiation.³³ By 3 months, 54% of patients receiving topical TRT and 37% of patients prescribed short-lasting TRT injections were still receiving treatment. After one year

after initiation of therapy, only 18% of topical TRT users and 5% of short-lasting TRT injection users were still continuing treatment. However, almost 60% of patients received TRT in a cyclic fashion. In general, these patients used TRT for a few months, stopped treatment for 2-3 months and then restarted TRT with the same dose and medication.

Other studies have found higher rates of adherence with testosterone products. For example, a chart review evaluated the subjective response rates and characteristics of 125 men treated with TRT. Initial mode of TRT was injectable in 55% of patients (n=70) and transdermal gel (AndroGel).²⁷ Approximately 60% of men (n=80) completed 12 months of therapy. Treatment was discontinued in 34 patients (26.8%) who reported no major benefit and 13 (10%) were lost to followup.²⁷ Adherence to TRT (specifically Testim) at 12 months was found to be 91% in another study.³⁴ No difference was observed in patients 65 years and older and those younger than 65 years of age. However, it should be noted that only 33% of men completed the follow-up period.

Summary

Information on adherence and/or persistence with testosterone replacement therapy has been inconsistent, with some studies showing poor adherence (i.e., 15% by 12 months) and other showing high adherence patterns (e.g., 91% after 12 months).

Testosterone Levels

Reference ranges for lower normal level of testosterone (percentile 2.5) have been compiled from three large community-based samples, suggesting a cut-off of 12.1 nmol/L for total serum testosterone and calculated free testosterone 243 pmol/L.³⁵ Levels should be taken in the morning, when levels are highest and best reproducible. In men aged 40-79 years, the threshold for total testosterone was 8 nmol/L for decreased frequency of sexual thoughts, 8.5 nmol/L for erectile dysfunction, 11 nmol/L for decreased frequency of morning erections and 13 nmol/L for diminished vigour.² Other studies have suggested that 10.4 nmol/L (300 ng/dL) is a threshold that can be used for the treatment of symptomatic men.³ In one study, the use of a 300 ng/dL threshold for total testosterone captured most symptoms identified as related to androgen deficiency.³⁶ Although total testosterone in serum is a suitable screening test for the diagnosis of hypogonadism in many men, if abnormalities in concentrations of sex-hormone-binding globulin are suspected, measurement of free or bioavailable testosterone is indicated.³ Lower thresholds for free testosterone range from 0.17 to 0.31 nmol/L, and depend on the method of measurement of free testosterone. Free testosterone measurements by analog methods (used in most laboratories in Ontario) are affected by alterations in sex hormone binding globulin (SHBG) and their use is not recommended.³⁷ It should be noted, that a decrease in testosterone levels is observed with age that is unrelated to illness. Levels begin to decline between the ages of 35 and 40 years, when there is on average, a 1-2% decline of total testosterone levels per year.^{1;10}

Most clinical guidelines recommend testosterone supplementation in patients with symptomatic, unequivocally low testosterone levels confirmed by repeated laboratory tests.^{2;11} Although there are few long-term RCTs of testosterone use in patients with classic hypogonadism, agreement exists that

men with these conditions should be treated.³⁸ However, controversy exists regarding the treatment of older men with lower testosterone levels, who may not fully meet diagnostic or symptomatic criteria for hypogonadism. In one study, 54% of patients in the UK who were initiated on testosterone did not have a total testosterone measurement in the 180 days before initiation, 33% had one test and the remaining had more than one test.³⁹ Men in the US had more testosterone tests immediately before initiation: 40% did not have a baseline test, 50% had one test, and the remaining had more than one test. Another study found that almost 25% of men prescribed testosterone in the US had not previously had a blood test to determine if their testosterone was low.⁴⁰

Summary

Controversy still exists regarding reference ranges for normal levels of testosterone. Most guidelines suggest that total testosterone level above 12 nmol/L does not require replacement; patients with serum levels below 8nmol/L will usually benefit from treatment.^{11;19} As well, it is recommended that testosterone levels be measured prior to commencement of treatment.

Health Canada and Food and Drug Administration (FDA) Alerts and Warnings

- Health Canada issued an information update on July 15, 2014 advising the community of new safety information regarding testosterone hormone replacement products and risk of serious and possible life-threatening cardiovascular problems.⁴¹ Health Canada completed a safety review and found evidence for serious and possible life-threatening cardiovascular problems. They noted that testosterone products:
 - Should not be used in men for non-specific symptoms if laboratory tests have not been done to confirm a low testosterone level and other possible causes for the symptoms have not been excluded
 - Should not be used in children under the age of 18 as safety and effectiveness has not been established in these patients
 - Should not be used by women
- FDA has added a general warning in the drug labeling of all approved testosterone products about the risk of blood clots in the veins.⁴² In addition, the FDA is investigating the risk of stroke, heart attack and death in men taking testosterone products.⁴³

Discussion

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability in Canada

- In Canada, testosterone is available as a long-acting injectable, oral product or topical product. There are two long-acting testosterone injectable products: testosterone cypionate and testosterone enanthate. Only one product is available as an oral product: testosterone undecanoate. Four topical products are commercially available: testosterone transdermal patch

(Androderm), testosterone 1% topical gel (Testim), testosterone 1% gel foil packet and pump (Androgel) and testosterone 2% topical solution (Axiron).

- The long-acting injectable testosterone cypionate and the oral testosterone (testosterone undecanoate) are available as generic products.
- The cost of a one-month supply for the oral generic product is \$17-51, for the injectable product \$29-51 and for the topical products \$60-200.

Public Plan Listing in Ontario

- In Ontario, available testosterone products (including oral, injectables, Androgel, Testim and Androderm) are listed as “limited use” products. Restriction criteria limit the use of the testosterone products for male patients with confirmed serum testosterone levels associated with documented, symptomatic hypothalamic, pituitary or testicular disease, or in HIV-infected patients.

Public Plan Listing in Canada

- Oral product: Six of the 12 (50%) public drug programs in Canada list oral testosterone undecanoate as a general benefit. In five jurisdictions, the oral product is available on a restricted basis, requiring special authorization. In Ontario it is listed as a Limited Use Product. One province (BC) does not list this product.
- Long-acting injectable: These products are available as a general benefit in 10 jurisdictions and restricted in two. In Ontario, these products are listed as Limited Use Products
- Topical products: No topical treatment is listed on the formulary of five (42%) jurisdictions. It is a restricted listing (enforced or passive) in six (50%), and a general benefit in one jurisdiction. Topical testosterone products are listed as Limited Use products in Ontario.
- Although restriction criteria vary among the public drug plans, most state that the testosterone products are indicated for treatment of congenital and acquired primary or secondary hypogonadism in males. Five jurisdictions state that these products are not considered for use in the treatment of androgen decline in the aging male.

Selected International Jurisdictions

- In the United States, many health plans restrict the use of testosterone products through a prior authorization process.
- In Australia, testosterone products (including topical, injectable, oral) are available through a Special Authorization process. In contrast, New Zealand funds testosterone patch (Androderm), testosterone injectable products and oral testosterone as a general listing.

Part B: Guidelines for the management of patients with hypogonadism

- Guidelines/consensus recommendations vary in the definition of normal testosterone levels. Three of the five reviews suggest that the lower normal range is 8-12 nmol/L (using total testosterone levels).
- Although four of the five guidelines/consensus recommendations suggest that diagnosis of hypogonadism is based on consistent symptoms and signs and low serum testosterone levels, there is no consensus regarding the number of signs/symptoms that must be present before making a

diagnosis.

- All guidelines suggest that choice of testosterone formulation should be based on numerous factors including patient's preference, treatment burden and cost, and should be made as a joint decision between patient and physician.

Part C: Impact of different drug reimbursement schemes for testosterone replacement therapy

- There is a lack of information detailing the impact of different drug reimbursement options for testosterone replacement therapies.
- A restriction policy (using Limited Use codes) in Ontario resulted in a temporary decrease in testosterone prescribing; however, testosterone use rose over 450% in the six years after implementation of the restriction policy suggesting that such a policy has minimal long-term effect testosterone use.

Part D: Rapid Reviews of Selected Topics

- *Choice of treatment for testosterone replacement therapies:* In Canada, testosterone is available as an oral formulation, as an intramuscular injectable agent and in various topical preparations including gels, patch and topical axillary solution. Selection of a product is based on the patient's preference, pharmacokinetics of the testosterone formulation, treatment burden, cost and safety profile.
- *Adherence to testosterone replacement therapies:* Information on adherence and/or persistence with testosterone replacement therapy has been inconsistent, with some studies showing poor adherence (i.e., 15% by 12 months) and other showing high adherence patterns (e.g., 91% after 12 months). In one study, TRT was used in a cyclic fashion (i.e., patients used TRT for a few months, stopped treatment for 2-3 months and then restarted TRT with the same dose and medication.)
- *Testosterone levels:* Controversy still exists regarding reference ranges for normal levels of testosterone. Most guidelines suggest that total testosterone level above 12 nmol/L does not require replacement; patients with serum levels below 8nmol/L will usually benefit from treatment. As well, it is recommended that testosterone levels be measured prior to commencement of treatment.

Health Equity

In Ontario, all testosterone formulations (with the exception of testosterone axillary topical solution) are available on the formulary as Limited Use products. No health equity issue was identified for patients with a diagnosis of classical hypogonadism .

Conclusion

Testosterone (injectable, oral, topical preparations with the exception of the axillary topical solution) is available on the ODB formulary as a Limited Use product for the treatment of patients with documented

and symptomatic hypothalamic, pituitary or testicular disease, or in HIV-infected patients.

Most public drug plans in Canada require special authorization prior to funding testosterone preparations. All jurisdictions in Canada fund the injectable product, most the oral product and two-thirds one or more of the topical products. Some international jurisdictions (e.g., Australia) restrict the use of these products via a special authorization process. However, there is a lack of literature assessing these more restrictive reimbursement strategies for adherence or outcome measures.

Reference List

- (1) Abadilla KA, Dobs AS. Topical testosterone supplementation for the treatment of male hypogonadism. *Drugs* 2012; 72(12):1591-1603.
- (2) Dohle G, Arver S, Bettocchi C, et al. Guidelines on male hypogonadism: European Association of Urology. http://www.uroweb.org/gls/pdf/16_Male_Hypogonadism_LR%20II.pdf. 2012
- (3) Basaria S. Male hypogonadism. *Lancet* 2014; 383:1250-1263.
- (4) Bain J, Brock G, Kuzmarov I. Canadian Society for the Study of the Aging Male: response to Health Canada's position paper on testosterone treatment. *The journal of sexual medicine* 2007; 4:558-566.
- (5) Morales A, Schulman C, Tostain J, Wu C. Testosterone deficiency syndrome (TDS) needs to be named appropriately: the importance of accurate terminology. *Eur Urol* 50, 407-409. 2006.
- (6) Gan EH, Pattman S, Pearce HS, Quinton R. A UK epidemic of testosterone prescribing, 2001-2010. *Clinical endocrinology* 2013; 79(4):564-570.
- (7) Mulligan T, Frick M, Zuraw QC, et al. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract* 2006; 60:762-769.
- (8) Wu F, Tajar A, Beynon J, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med* 2010; 363:123-135.
- (9) Araujo A, O'Donnell A, Brambilla D, et al. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. *The Journal of clinical endocrinology and metabolism* 2004; 89:5920-5926.
- (10) Nigro N, Christ-Crain M. Testosterone treatment in the aging male: myth or reality? *Swiss medical weekly* 2012; 142.
- (11) Bhasin S, Cunningham G, Hayes F, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism* 2010; 95.
- (12) Ontario Ministry of Health and Long-term Care. The Narcotics Safety and Awareness Act, 2010. http://www.health.gov.on.ca/en/public/programs/drugs/ons/ons_legislation.aspx. 2012
- (13) Ovsag K, Hyder S, Mousa S. Preferred drug lists: potential impact on healthcare economics. *Vascular health and risk management* 2008; 4:403-413.
- (14) Motheral B, Fairman K. Effect of a three-tier prescription copay on pharmaceutical and other medical utilization. *Med Care* 2001; 39:1293-1304.

- (15) Australian Government Department of Health. Pharmaceutical Benefits Scheme. Australian Government Department of Health [2013 Available from:
URL:<http://www.pbs.gov.au/browse/body-system>
- (16) Handelsman DJ. Global trends in testosterone prescribing, 2000-2011: expanding the spectrum of prescription drug misuse. *Med J Aust* 2013; 199(8):548-551.
- (17) PHARMAC. PHARMAC: Pharmaceutical Management Agency for New Zealand. <http://www.pharmac.health.nz>. 2014
- (18) Scottish Medicines Consortium. SMC Advice Directory. http://www.scottishmedicines.org.uk/SMC_Advice/Advice_Directory/SMC_Advice_Directory?ds=Y&searchtext=symbicort&category=&submissionType=&fromDate=From%3A&toDate=To%3A&acceptedForUseCheck=Y&acceptedForRestrictedUseCheck=Y¬RecommendedForUseCheck=Y 2013
- (19) Wang C, Nieschlag E, Swerdloff R, et al. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. *The aging male : the official journal of the International Society for the Study of the Aging Male* 2009; 12:5-12.
- (20) Wylie K, Rees M, Hackett G, et al. Management of sexual problems in men: the role of androgens. http://bssm.org.uk/downloads/UK_Guidelines_Androgens_Male_2010.pdf . 2010.
- (21) Morales A, Bella A, Chun S, et al. A practical guide to diagnosis, management and treatment of testosterone deficiency for Canadian physicians. *Can Urol Assoc J* 2010; 4:269-275.
- (22) Clay PG. Program savings associated with switching testosterone intramuscular injections to topical gel in HIV infected males. *Curr Med Res Opin* 2004; 20(4):461-468.
- (23) Piszczek J, Mamdani M, Antoniou T, Juurlink DN, Gomes T. The Impact of Drug Reimbursement Policy on Rates of Testosterone Replacement Therapy among Older Men. *PLoS One* 2014; 9(7):e98003.
- (24) Kovac JR, Rajanahally S, Smith RP, Coward RM, Lamb DJ, Lipshultz LI. Patient satisfaction with testosterone replacement therapies: the reasons behind the choices. *The journal of sexual medicine* 2014; 11(2):553-562.
- (25) Corona G, Rastrellia G, Forti G, Maggi M. Update in testosterone therapy for men. *J Sex Med* 8, 639-654. 2011.
- (26) Seftel A. Testosterone replacement therapy for male hypogonadism: Part III. Pharmacologic and clinical profiles, monitoring, safety issues, and potential future agents. *Int J Impot Res* 2007; 19:2-24.
- (27) Rhoden EL, Morgentaler A. Symptomatic response rates to testosterone therapy and the likelihood of completing 12 months of therapy in clinical practice. *The journal of sexual medicine*

- 2010; 7(1 Pt 1):277-283.
- (28) Gooren L. A ten-year safety study of the oral androgen testosterone undecanoate. *J Andrology* 1994; 15:212-215.
- (29) Kunz G. Virilization of young children after topical androgen use by their parents. *Pediatrics* 114, 282-284. 2004.
- (30) Grober ED, Khera M, Soni SD, Espinoza MG, Lipshultz LI. Efficacy of changing testosterone gel preparations (Androgel or Testim) among suboptimally responsive hypogonadal men. *Int J Impot Res* 2008; 20(2):213-217.
- (31) Schoenfeld MJ, Shortridge E, Cui Z, Muram D. Medication adherence and treatment patterns for hypogonadal patients treated with topical testosterone therapy: a retrospective medical claims analysis. *The journal of sexual medicine* 2013; 10(5):1401-1409.
- (32) Ho P, Bryson C, Rumsfeld J. Medication adherence: its importance in cardiovascular outcomes. *Circulation* 119, 3028-3035. 2009.
- (33) Donatucci C, Cui Z, Fang Y, Muram D. Long-term treatment patterns of testosterone replacement medications. *The journal of sexual medicine* 2014; 11(8):2092-2099.
- (34) Bhattacharya RK, Khera M, Blick G, Kushner H, Miner MM. Testosterone replacement therapy among elderly males: the Testim Registry in the US (TRIUS). *Clin Interv Aging* 2012; 7:321-330.
- (35) Bhasin S, Pencina M, Jasuja G, et al. Reference ranges for testosterone in men generated using liquid chromatography tandem mass spectrometry in a community-based sample of healthy nonobese young men in the Framingham Heart Study and applied to three geographically distinct cohorts. *The Journal of clinical endocrinology and metabolism* 2011; 96:2430-2439.
- (36) Hall S, Esche G, Araujo A, et al. Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. *The Journal of clinical endocrinology and metabolism* 2008; 93:3870-3877.
- (37) Bhasin S, Cunningham G, Hayes F, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism* 2010; 95:2536-2539.
- (38) Spitzer M, Huang G, Basaria S, Travison TG, Bhasin S. Risks and benefits of testosterone therapy in older men. *Nature reviews Endocrinology* 2013; 9:414-424.
- (39) Layton JB, Li D, Meier CR, Sharpless JL, Sturmer T, Jick SS et al. Testosterone lab testing and initiation in the United Kingdom and the United States, 2000 to 2011. *The Journal of clinical endocrinology and metabolism* 2014; 99(3):835-842.
- (40) Baillargeon J, Urban R, Ottenbacher K, et al. Trends in androgen prescribing in the United States,

2001 to 2011. JAMA Intern Med 173, 1465-1466. 2013.

- (41) Health Canada. Information update: possible cardiovascular problems associated with testosterone products. <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/40587a-eng.php>. 2014
- (42) US Food and Drug Administration. FDA adding general warning to testosterone products about potential for venous blood clots. <http://www.fda.gov/drugs/drugsafety/ucm401746.htm>. 2014
- (43) US Food and Drug Administration. FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products. <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM383909.pdf>. 2014
- (44) New Brunswick Department of Health. New Brunswick Prescription Drug Program Formulary. <http://www.gnb.ca/0212/nbpdpformulary-e.asp>. 2013
- (45) Nova Scotia Pharmacare. Nova Scotia Formulary. <http://novascotia.ca/dhw/pharmacare/formulary.asp>. 2013
- (46) PEI Pharmacare. Formulary. <http://healthpei.ca/formulary>. 2013
- (47) Newfoundland and Labrador Department of Health and Community Services. Newfoundland and Labrador Interchangeable Drug Products Formulary. <http://www.health.gov.nl.ca/health/nlpdp/fmlsearch.asp>. 2013

Appendix 1: Restriction Criteria for Testosterone Products in Canada

Province	Criteria
Alberta	<p>Androderm, testosterone undecanoate (Andriol)</p> <p>For use in males for the treatment of congenital and acquired primary and secondary hypogonadism. Coverage cannot be considered when used for the treatment of androgen decline in the aging male (ADAM).</p> <p>Special authorization may be granted for 6 months.</p>
British Columbia	<p>For the treatment of testosterone deficiency in one of the following diagnoses: Hypogonadism OR Orchiectomy OR Undescended testes OR Klinefelter's syndrome OR Female-to-male (gender) transformation OR Pituitary tumour OR Removal of pituitary gland OR</p> <p>For the indication of: Surgery of pituitary gland AND where low testosterone levels have been documented OR AIDS-wasting syndrome AND where low testosterone levels have been documented.</p>
Ontario	<p>LU Code 397: For male patients with confirmed low morning serum testosterone levels associated with documented, symptomatic hypothalamic, pituitary or testicular disease, or in HIV-infected patients.</p> <p>Note: Older males with nonspecific symptoms of fatigue, malaise, depression who have a low normal random testosterone level do not satisfy these criteria.</p> <p>LU Authorization Period: 1 year</p>
New Brunswick⁴⁴	<p>TESTOSTERONE (ANDRODERM, ANDROGEL, TESTIM) 12.2mg and 24.3mg patches, 2.5g and 5g packets, 1% gel TESTOSTERONE UNDECANOATE (ANDRIOL and generic brand) 40 mg capsules</p> <p>For the treatment of congenital and acquired primary or secondary hypogonadism in males with a specific diagnosis of:</p> <ul style="list-style-type: none"> • Primary: cryptorchidism, Klinefelter's, orchiectomy, and other established causes • Secondary: Pituitary-hypothalamic injury due to tumors, trauma, radiation <p>Testosterone deficiency should be clearly demonstrated by clinical features and confirmed by two separate free testosterone measurements before initiating any replacement therapy</p> <p>Note: Older males with non-specific symptoms of fatigue, malaise, or depression who have low testosterone levels do not satisfy these criteria.</p>
Nova Scotia⁴⁵	<p>TESTOSTERONE, TOPICAL (Androderm Patch, Androgel Gel Packet & Testim Gel)</p> <p>For the treatment of congenital and acquired primary or secondary hypogonadism in males with a specific diagnosis of:</p> <ul style="list-style-type: none"> • Primary: cryptorchidism, Klinefelter's, orchidectomy, and other established causes • Secondary: pituitary-hypothalamic injury due to tumors, trauma, radiation • deficiency should be clearly demonstrated by clinical features and confirmed by two separate biochemical tests before initiating any therapy <p>NOTE: Maximum dose approved is 5g per day or a 5mg patch per day. by limiting the quantity payable each quarter (e.g. Jan-Mar) to: 120 Androderm Patches (2.5mg or 5mg Patch); · 300g of Androgel 2.5g gel (packet); or · 600g of Testim Gel</p>

PEI ⁴⁶	<p>Testosterone, transdermal gel, 25mg/2.5gm packet, 50mg/5gm packet (AndroGel-ABB); 50mg/5gm tube (Testim-PAL)</p> <p>Note: Not interchangeable.</p> <p>For the treatment of congenital and acquired primary or secondary hypogonadism in males with a specific diagnosis of;</p> <ul style="list-style-type: none"> • Primary - Cryptorchidism, Klinefelter's, orchiectomy, and other established causes. • Secondary - Pituitary-hypothalamic injury due to tumors, trauma, radiation. <p>Testosterone deficiency should be clearly demonstrated by clinical features and confirmed by two separate biochemical tests before initiating any testosterone therapy. Limited to 5 g/day gel.</p> <p>Older males with non-specific symptoms of fatigue, malaise or depression who have low testosterone (T) levels do not satisfy these criteria.</p> <p>Testosterone Undecanoate, capsule, 40mg (Andriol-MSD)</p> <p>For patients with a documented deficiency in whom treatment with depo-testosterone products have been unsuccessful, intolerable or are medically contraindicated.</p>
Yukon	<p>Coverage for hormonal replacement required for an approved chronic condition (e.g. primary hypogonadism, pituitary disorders). Cases reviewed individually.</p>
Newfoundland ⁴⁷	<p>Testosterone Undecanoate (Andriol 40mg capsule and generics) Testosterone topical (AndroGel 2.5mg & 5mg sachets, Testim 1% gel, Androderm 25mg/24hr, 50mg/24hr patch)</p> <p>For the treatment of congenital and acquired primary or secondary hypogonadism in males with a specific diagnosis of:</p> <ul style="list-style-type: none"> • Primary: Cryptorchidism, Klinefelter's, orchiectomy, and other established causes. • Secondary: Pituitary-hypothalamic injury due to tumors, trauma, radiation. <p>Testosterone deficiency should be clearly demonstrated by clinical features and confirmed by two separate biochemical tests before initiating any T therapy.</p> <p>Older males with non-specific symptoms of fatigue, malaise or depression who have low testosterone (T) levels do not satisfy these criteria.</p> <p>Limited to 5 g/day gel or 5 mg patch. (for topical products)</p>

Appendix 2: Webpages for Provincial Drug Formularies

Province	Webpage for Drug Formulary
British Columbia	http://www.health.gov.bc.ca/pharmacare/benefitslookup/faces/Search.jsp
Alberta	https://idbl.ab.bluecross.ca/
Saskatchewan	http://formulary.drugplan.health.gov.sk.ca/
Manitoba	http://web6.gov.mb.ca/eFormulary/
Ontario	https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp
Quebec	http://www.ramq.gouv.qc.ca/en/regie/legal-publications/Pages/list-medications.aspx
New Brunswick	http://www.gnb.ca/0212/nbpdpformulary-e.asp
Nova Scotia	http://novascotia.ca/dhw/pharmacare/formulary.asp
Prince Edward Island	http://healthpei.ca/formulary
Newfoundland	http://www.health.gov.nl.ca/health/nlmdp/fmlsearch.asp
Yukon Territories	https://apps.gov.yk.ca/pls/apex40p/f?p=161:9000:4324580815029961::::
NIHB (Non-insured Health Benefits) Program	http://www.hc-sc.gc.ca/fniah-spnia/nihb-ssna/provide-fourdir/pharma-prod/med-list/index-eng.php

Appendix 3: Interview Questions

How long have you listed testosterone products on your provincial formulary? How are they listed (e.g., restricted, general benefit)?
Why did you decide to list TRTs this way?
What was the basis for this listing (e.g., quantity limits, general listing)?
Do you have any studies comparing usage/costs before and after implementation of this listing?
Why are certain TRTs NOT funded?
Do you restrict prescribing to certain specialties (or are certain specialties exempt from restrictions)?

Appendix 4: Tiered cost-sharing options

Prescription Drug Plan	Tier 1 (generic)	Tier 2 (preferred brand)	Tier 3 (non-preferred brand)	Tier 4 (specialty)
Plan A	\$5	\$28	\$55	25%
Plan B	\$2	\$20	\$40	N/A
Plan C	\$10	\$25	50%	25%
Plan D	\$4	\$17	75%	25%

Adapted from:

<http://www.cancer.org/treatment/findingandpayingfortreatment/managinginsuranceissues/medicare/medicarepartd/medicare-part-d-formularies-and-drug-coverage>