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This report and the French version entitled Analyse clinique et économique de l’emploi du tériparatide et des bisphosphonates dans le traitement de l’ostéoporose féminine are available on CADTH’s web site.

Production of this report is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon. The Canadian Agency for Drugs and Technologies in Health takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada or any provincial or territorial government.

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CADTH is funded by Canadian federal, provincial, and territorial governments.

Legal Deposit - 2006
National Library of Canada
ISBN: 1-897257-57-0 (online)
H0301 – October 2006

PUBLICATIONS MAIL AGREEMENT NO. 40026386
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Teriparatide and Bisphosphonates for Treatment of Osteoporosis in Women: A Clinical and Economic Analysis

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Authorship

Douglas Coyle was the principal investigator, and was involved in all aspects of the project. He was responsible for the design, analysis, and writing of the primary economic analysis, the economic literature search, and the review of economic studies.

Abdallah Hadj Tahar was involved in all aspects of the project related to the clinical review. He wrote the introduction and clinical review, and provided input to all drafts.

Gaetanne Murphy was responsible for the write-up of the budget impact analysis and executive summary, and contributed to revisions of other sections. She coordinated the project during the review and editing stages.
Christine Perras wrote the discussion and conclusion, and contributed to other sections. She reviewed draft versions of the report, and approved the final version.

Becky Skidmore was responsible for the design and execution of the literature search strategies for the clinical review, for writing the methods section and associated appendix on literature searching, and for verifying and formatting the bibliographic references.

Michel Boucher contributed to the introduction, clinical review, and discussion sections of the report. He reviewed draft versions of the report, and approved the final version.

Don Huseineau contributed to the design and writing of the research protocol. He provided input to subsequent drafts of the report.

Acknowledgements

The authors gratefully acknowledge Rhonda Boudreau for her assistance with the editing of the report. Rhonda is a Research Officer in the Health Technology Assessment Directorate of CADTH.

Conflicts of Interest

Doug Coyle has undertaken research that was sponsored by Eli Lilly, but that was unrelated to the topic of this report.
Teriparatide and Bisphosphonates for Treatment of Osteoporosis in Women: a Clinical and Economic Analysis

Technology and Condition
Bisphosphonates (alendronate, etidronate, risedronate) and teriparatide for prevention of fracture in postmenopausal women.

Issue
Osteoporosis is associated with significant disease burden. Effective therapies for osteoporosis are attractive, because their acquisition costs may be offset by future savings associated with fracture prevention. There is a need to assess the value in funding these drugs, given their considerable use and cost with an aging Canadian population.

Methods and Results
A systematic review of the clinical literature was done to compare teriparatide to bisphosphonates or placebo. Net health impact was estimated using a decision-analytic model in terms of quality-adjusted life years (QALYs). An economic evaluation compared teriparatide to bisphosphonates, or no drug therapy. The base-case for this analysis was an 80-year-old woman with at least one previous osteoporotic fracture. The budget impact of funding teriparatide and bisphosphonates in public drug plans was also assessed.

Implications for Decision Making
- **Alendronate or no drug therapy are optimal.** Etidronate, risedronate, and teriparatide were more costly and less effective than alendronate.
- **Etidronate is not cost effective.** Etidronate was more costly and less effective than both drug and no drug therapy options in all scenarios. Switching from etidronate to generic alendronate would cost an additional C$50 per patient every year.
- **Cost effectiveness depends on age.** Compared to no drug therapy, alendronate costs an additional C$169,600 per QALY for a 65-year-old woman. In a 90-year-old, alendronate therapy is less costly and more effective than no drug therapy.
- **Publicly funding teriparatide would require an additional C$115 million in 2006.** This assumes 2.5% of current bisphosphonate users would be switched to teriparatide.

This summary is based on a comprehensive health technology assessment available from CADTH’s web site (www.cadth.ca): Coyle D, Hadj Tahar A, Murphy G, Perras C, Skidmore B, Boucher M, Husereau D. *Teriparatide and bisphosphonates for treatment of osteoporosis in women: a clinical and economic analysis*
EXECUTIVE SUMMARY

The Issue
The prevention of osteoporotic fractures is a public health priority in Canada. Osteoporosis is associated with medical, social, and financial implications. As the Canadian population ages, the incidence of osteoporosis is expected to increase.

Pharmacological interventions that are used to treat osteoporosis include the bisphosphonates (alendronate, etidronate, and risedronate), the specific estrogen receptor modulator raloxifene, and the parathyroid hormone analogue (1-34) teriparatide. In a previous CCOHTA report, raloxifene’s primary clinical effect was found to be in the secondary prevention of vertebral fractures in older postmenopausal women. This effect, however, was offset by a similar increase in serious adverse events due to venous thrombo-embolic disease. In a recent CADTH report, bisphosphonates were found to be effective mainly in the secondary prevention of osteoporotic fractures. Teriparatide is a more recently approved drug with a price several times higher than that of other interventions. There is uncertainty about the relative health, economic, and fiscal impact of its use relative to other effective prescription drug treatments.

Objective
The aim of this report is to assess the clinical and cost effectiveness of teriparatide relative to the bisphosphonates for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. The clinical analysis will compare teriparatide to bisphosphonates or placebo, and the economic analysis will compare teriparatide to bisphosphonates or no drug therapy. The report will also assess the budget impact of funding teriparatide and the bisphosphonates by publicly funded drug plans.

Clinical Review of Effectiveness
Methods: A systematic review of available literature for randomized controlled trials of teriparatide was conducted using a standardized Cochrane Collaboration approach to literature search, article selection, data extraction, and quality assessment. The results of a similarly conducted previous systematic review by CADTH were used to estimate the health impact of using bisphosphonates.

Results: Two teriparatide trials met the selection criteria. In these studies, teriparatide was evaluated for the secondary prevention of osteoporosis. It was not feasible to pool study data for analysis, because the trials used different comparison groups.

One trial indicated that teriparatide, at 20 micrograms or 40 micrograms per day administered subcutaneously, reduces the risk of vertebral and non-vertebral fractures, compared with placebo. Non-vertebral fractures included a pooled analysis of all fracture sites other than the vertebrae. Patients treated with teriparatide 40 micrograms per day had a higher rate of withdrawal due to adverse events than patients in the placebo group. The other trial compared teriparatide 40 micrograms per day with oral alendronate 10 mg per day, and reported no difference in the rate of non-vertebral fractures. There were no differences between the two agents in withdrawals due to adverse events or any cause.
The previous CADTH review of bisphosphonates identified 28 trials that met the selection criteria. RCTs were categorized as primary or secondary prevention, based on the absence or presence of pre-existing fractures, or on BMD. Meta-analyzed data from 11 etidronate RCTs (1,248 women), 11 alendronate RCTs (12,099 women) and six risedronate RCTs (13,795 women) were used to estimate the impact on fractures and adverse events. Seven RCTs (three etidronate, three alendronate, one risedronate) were primary prevention trials.

Evidence from the CADTH review indicates that the main benefits of bisphosphonate therapy, relative to placebo, lie in the secondary prevention of osteoporotic fractures (i.e., the prevention of fractures in patients with a BMD=2 standard deviations below the peak bone mass or with pre-existing osteoporotic fractures). The magnitude of this effect varies among bisphosphonates. Etidronate is associated with a reduction in vertebral fractures. Risedronate reduces vertebral, hip, and non-vertebral fractures. Alendronate was associated with reductions in vertebral, non-vertebral, hip, and wrist fractures, although statistical significance was only reached for wrist fractures when a yearly fixed-effect analysis was applied. Available data suggested no statistically significant differences in the rates of drop-out or discontinuation due to adverse events between bisphosphonate and placebo recipients in clinical trials.

Indirect comparisons with the bisphophonates suggest that teriparatide is more effective in the secondary prevention of vertebral fractures, whereas alendronate is more effective in reducing hip and wrist fractures.

**Economic Analysis**

**Methods:** The cost effectiveness of teriparatide 20 micrograms per day was assessed using a decision-analytic model in women with osteoporotic fractures at ages 65, 70, 80, and 90 years. Teriparatide was compared with alendronate, etidronate, risedronate, and no drug therapy.

The health-care system perspective was used for the analysis, and to approximate the societal perspective. The decision-analytic model reflected the natural history of women with osteoporosis, incorporating the sequelae (e.g., fracture) and the transition of women in terms of the development of osteoporosis, history of fracture, and residential status (e.g., admission to a long-term care facility). A sensitivity analysis was conducted to assess the robustness of the study results.

**Results:** The base case analysis for an 80-year-old woman with a previous osteoporotic fracture showed that alendronate was the most cost-effective treatment. Risedronate and teriparatide were dominated by alendronate; etidronate was dominated by no drug therapy. A treatment is dominated by another if it is more costly and less effective; i.e., no matter what the willingness to pay for a health outcome, the treatment will not be cost-effective. The incremental cost effectiveness ratio for alendronate versus no drug therapy was C$13,000 per quality-adjusted life-year (QALY) gained for an 80-year-old, and increased to C$169,600 for a 65-year-old woman. The sensitivity analysis showed that the results did not significantly change even when additional analyses were conducted using different discount rates, baseline risk characteristics, and assumptions about drug costs, dosage forms, compliance, and benefit beyond therapy curtailment.
Health Services Impact

A budget impact analysis was prepared to determine the incremental cost of adding teriparatide as a limited use benefit to publicly funded drug plans (i.e., if 2.5% to 5% of current bisphosphonate patients were switched to teriparatide). Drug plans would then incur an additional C$115 million to C$230 million in drug costs in 2006, depending on the utilization and the number of patients treated.

Conclusions

Clinical

- Compared with placebo, teriparatide 20 micrograms administered daily by subcutaneous injection confers a significant reduction in the risk of vertebral and non-vertebral fractures as secondary prevention.
- Teriparatide 40 micrograms daily and alendronate 10 mg daily are not significantly different in the secondary prevention of non-vertebral fractures.
- Teriparatide 20 micrograms per day, the recommended dose, has not been compared in head-to-head fracture trials with any bisphosphonate.
- No trials with teriparatide studied the primary prevention of osteoporotic fractures in women.
- Limited evidence support the use of bisphosphonates in the primary prevention of osteoporotic fractures. Only alendronate has been shown to be effective in primary prevention, and this effect is limited to vertebral fractures.
- Compared with placebo, etidronate is effective in the secondary prevention of vertebral fractures.
- Compared with placebo, alendronate is effective in the secondary prevention of vertebral, non-vertebral, hip, and wrist fractures.
- Compared with placebo, risedronate is effective in the secondary prevention of vertebral, non-vertebral, and hip fractures.

Economic

- Alendronate or no drug therapy is the optimal treatment option. The choice between the two depends on the woman’s age (i.e., alendronate is more cost-effective for women ≥80 years because of an increase in the baseline risk of fracture), and the maximum willingness of decision makers to pay for a QALY gained (e.g., ICER of C$169,600 for alendronate versus no drug therapy among women 65 years of age).
- Teriparatide is not cost-effective compared to bisphosphonates under any scenario.
- If no drug therapy is the only available alternative, then teriparatide in an 80-year-old woman with a previous fracture is cost-effective if the health care system is prepared to pay C$851,000 for a QALY.
- Etidronate was dominated by alendronate in all age groups.
- It is estimated that by 2006, if teriparatide were listed as a limited use benefit on publicly funded drug plans, governments could incur C$115 million to C$230 million in additional drug costs, depending on the utilization, and the number of patients treated.
ABBREVIATIONS

ARR  absolute risk reduction
BMD  bone mineral density
CEA  cost effectiveness analysis
CEAC cost effectiveness acceptability curves
CI  confidence interval
CUA  cost-utility analysis
DIN  drug identification number
HRT  hormone replacement therapy
ICUR  incremental cost-utility ratio
LTC  long-term care
MCS  Monte Carlo simulation
NA  not applicable
NE  not estimable
NNT  number needed to treat
PTH  parathyroid hormone
QALY quality-adjusted life-year
RCT  randomized controlled trial
RR  relative risk
RRR  relative risk reduction
SD  standard deviation
US  United States
WHO  World Health Organization
YSM  years since menopause
# TABLE OF CONTENTS

**EXECUTIVE SUMMARY** ........................................................................................................ iv

**ABBREVIATIONS** ............................................................................................................... vii

**TABLE OF CONTENTS** ..................................................................................................... viii

1 **INTRODUCTION** ........................................................................................................... 1
   1.1 Background ................................................................................................................ 1
   1.2 Overview of the Technology ................................................................................... 1

2 **THE ISSUE** .................................................................................................................. 2

3 **OBJECTIVES** ............................................................................................................... 3

4 **CLINICAL REVIEW: TERIPARATIDE** ......................................................................... 3
   4.1 Methods .................................................................................................................. 3
   4.1.1 Literature search strategy ............................................................................... 3
   4.1.2 Selection criteria and method ........................................................................ 4
   4.1.3 Data extraction strategy ................................................................................ 4
   4.1.4 Strategy for quality assessment ................................................................... 5
   4.1.5 Data analysis methods ................................................................................... 5
   4.2 Results ................................................................................................................... 5
   4.2.1 Quantity of research available ....................................................................... 5
   4.2.2 Trial characteristics ....................................................................................... 5
   4.2.3 Data analysis and synthesis ........................................................................... 6
   4.3 Systematic Review of Bisphosphonates ............................................................... 9
   4.4 Discussion ............................................................................................................. 9

5 **ECONOMIC ANALYSIS** .............................................................................................. 10
   5.1 Review of Economic Studies .............................................................................. 10
   5.1.1 Methods .......................................................................................................... 10
   5.1.2 Study results ................................................................................................... 11
   5.1.3 Study quality .................................................................................................. 11
   5.2 Primary Economic Evaluation ............................................................................. 12
   5.2.1 Methods .......................................................................................................... 12
   5.2.2 Results ............................................................................................................ 19
   5.2.3 Discussion ....................................................................................................... 20

6 **HEALTH SERVICES IMPACT** ..................................................................................... 22
   6.1 Population Impact ................................................................................................. 22
   6.2 Budget Impact Assessment .................................................................................. 23
   6.2.1 Methods .......................................................................................................... 23
   6.2.2 Results ............................................................................................................. 27

7 **DISCUSSION** .............................................................................................................. 29
   7.1 Summary of Results ............................................................................................. 30
   7.1.1 Systematic Review of Teriparatide ................................................................. 30
   7.1.2 Systematic Review of Bisphosphonates .......................................................... 30
   7.1.3 Economic Evaluation ...................................................................................... 30
7.2 Study Limitations.............................................................................................. 31
7.3 Ability to Generalize Findings........................................................................... 32
7.4 Health Services Impact .................................................................................... 33
7.5 Knowledge Gaps.............................................................................................. 33

8 CONCLUSION........................................................................................................... 33

9 REFERENCES........................................................................................................... 35

APPENDICES - available from CADTH's web site www.cadth.ca

APPENDIX 1: Literature Search Strategy
APPENDIX 2: Data Extraction Form
APPENDIX 3: Quality Assessment Form
APPENDIX 4: Assessment of Allocation Concealment
APPENDIX 5: Figures
APPENDIX 6: Tables
1 INTRODUCTION

1.1 Background

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to increased bone fragility and a consequent increase in risk of fracture. The most common clinical manifestations in women who have osteoporosis are fractures of the hip, vertebrae, or wrist. The major source of morbidity from osteoporosis arises from hip fractures.

Approximately 30% of postmenopausal women have osteoporosis, according to the World Health Organization’s (WHO) definition of osteoporosis. Osteoporosis-related morbidity is associated with medical and social consequences. The risk of hip fracture increases as women age. Because of changing demographics, it is estimated that by 2040, the current number of hip fractures in Canada will triple. Evidence indicates there is a 20% mortality excess associated with osteoporotic hip fracture, and that mortality after a fracture is exponentially associated with age. It is unclear if this exponential increase results from the fracture, or if it is secondary to underlying or comorbid medical conditions.

Osteoporosis is associated with a large financial burden in Canada. A Canadian study estimated that in 1993, total costs exceeded C$1.3 billion. Canadian health-care costs associated with osteoporosis were C$465 million, with an additional C$563 million for long-term care (LTC) facilities and C$279 million for chronic care hospitals. Therapies intended to reduce the risk of osteoporosis-related fractures and their consequences can be attractive, because part of their acquisition costs may be offset by future savings associated with fracture prevention.

1.2 Overview of the Technology

The most commonly prescribed therapies for osteoporosis are bisphosphonates, calcium, and vitamin D supplements. Bisphosphonates are stable analogues of pyrophosphates that inhibit bone resorption through their effects on osteoclasts (i.e., cells associated with absorption and removal of bone). Three bisphosphonates are licensed for the treatment of osteoporosis in Canada: alendronate, etidronate, and risedronate. The typical daily doses are 10 mg for alendronate and 5 mg for risedronate. Both drugs can also be given weekly at a dose of 70 mg and 35 mg respectively. Etidronate is taken cyclically: a 400 mg tablet is taken every day for 14 days, followed by 76 days of calcium supplements (500 mg). The calcium supplements are included in the prescription package. This cycle is repeated four times annually. The cyclic administration of etidronate is recommended to prevent a complication called osteomalacia, which leads to bone softening or impaired mineralization and increased risk of fractures. In Canada, the daily drug costs for the bisphosphonates vary from C$0.40 to C$2.00 (Appendix 6 Table 1).

In 1999, etidronate made up 49% of prescriptions and 35% of bisphosphonate sales, and alendronate made up 51% of prescriptions and 65% of sales. In 2004, etidronate ranked third (with 20% of prescriptions and 15% of sales). Alendronate maintained its lead (with 51% of prescriptions and 54% of sales). Risedronate received Health Canada market approval in August 2000, and by 2004, ranked second with 31% of sales and 29% of bisphosphonate prescriptions (Appendix 5 Figures 1 and 2).
Teriparatide and bisphosphonates for treatment of osteoporosis in women: a clinical and economic analysis

The use of bisphosphonates in Canada has steadily increased over the past five years, progressing from 1.5 million prescriptions dispensed in 1999 to over five million in 2004. The sales of bisphosphonates increased from C$98.6 million in 1999 to C$312.2 million in 2004. This represents a market expansion of >200% over five years (Appendix 5 Figures 1 and 2).

Teriparatide is a synthetic, recombinant polypeptide hormone consisting of the first 34 amino acids of human parathyroid hormone (PTH). Its anabolic effects are thought to mimic the action of endogenous PTH, to stimulate new bone formation. The physiologic actions of endogenous PTH include regulation of bone metabolism, renal tubular resorption of calcium and phosphate, and intestinal calcium absorption. Continuous PTH may be detrimental to the skeleton by increasing bone resorption, as seen with primary hyperparathyroidism, but intermittent administration results in increased bone formation.

In Canada, teriparatide (Forteo® by Eli Lilly, DIN 02254689) is available in a 750 micrograms/3 mL pre-filled pen for injection. It received Notice of Compliance from Health Canada on June 3, 2004. It is indicated for the treatment of postmenopausal women with severe osteoporosis who are at risk of fracture, or who have failed with or are intolerant to previous osteoporosis therapy. It is also indicated to increase bone mass in men with primary or hypogonadal severe osteoporosis, who have failed with or are intolerant to previous osteoporosis therapy. The recommended dose is 20 micrograms by subcutaneous injection once daily in the thigh or abdomen, for a maximum lifetime treatment exposure of 18 months. Adverse effects that have been noted by the manufacturer include orthostatic hypotension and hypercalcemia. The product monograph contains a warning that in rats, teriparatide was associated with a dose- and duration-dependent increase in the incidence of osteosarcoma. The pen must be refrigerated and can be reused for 28 days. One pen costs C$742, for a daily cost of $26.50 (20 micrograms/day).

2 THE ISSUE

The prevention of osteoporotic fractures is a public health priority in Canada. The incidence of osteoporosis is expected to increase as the Canadian population ages (i.e., the proportion of Canadians who are 65 years and older is expected to increase from 13% in 2004 to 25% by 2041). The condition affects women and men to different degrees, and the management of these patients is associated with medical, social, and financial implications. The medical complications of hip (primarily), wrist, and vertebral fractures can cause significant morbidity and mortality. Reports show that of women who sustain a hip fracture, 50% will become dependent on others for their daily activities; a third will be discharged to nursing homes; and in older women, excess mortality in the first year may be as high as 20%. The financial burden is significant, exceeding C$1 billion across all health care sectors. Many consequences of osteoporosis are potentially preventable through the use of non-pharmacological and pharmacological interventions.

The pharmacological interventions used in osteoporosis include bisphosphonates (i.e., alendronate, etidronate, and risedronate), the specific estrogen receptor modulator raloxifene, and the PTH analog teriparatide. The effects of raloxifene and bisphosphonates were evaluated in a CCOHTA report and a CADTH report. Compared to placebo, raloxifene’s primary clinical benefit is the secondary prevention of vertebral fractures in older postmenopausal women. This effect is offset by a similar increase in serious adverse events due to venous thromboembolic disease. Bisphosphonates are
effective mainly in the secondary prevention of osteoporotic fractures; evidence also shows that alendronate is effective for the primary prevention of vertebral fractures.\textsuperscript{17}

Since the bisphosphonates entered the Canadian market, the use of these drugs has increased, with sales exceeding C$300 million in 2004. With the recent addition of teriparatide to the Canadian market, the drug costs to treat osteoporosis could increase further. Given the considerable use and cost of these drugs, there is a need to assess the cost effectiveness of therapies for osteoporosis, to aid decision makers in determining the value in funding these drugs. This report will build on existing CCOHTA and CADTH systematic reviews to assess the clinical and cost effectiveness of teriparatide, compared with placebo and to bisphosphonates in postmenopausal women with osteoporosis.

### 3 OBJECTIVES

The aim of this report is to assess the clinical and cost effectiveness of teriparatide compared with the bisphosphonates (alendronate, etidronate, and risedronate), for the primary and secondary prevention of osteoporosis-related fractures in postmenopausal women.

The objectives are to:
- conduct a systematic review of studies evaluating the clinical effectiveness of teriparatide in the prevention of osteoporotic fractures, compared with a placebo or a bisphosphonate
- evaluate the cost effectiveness of teriparatide, compared with a bisphosphonate or no drug therapy
- conduct a budget impact analysis of funding teriparatide and the bisphosphonates from the perspective of publicly funded drug plans.

For the economic evaluation, the analysis was conducted using only Canadian data. The analytic model has been used in several previous studies to evaluate treatments for osteoporosis.\textsuperscript{18-21} Data on the clinical effectiveness of the three bisphosphonate drugs are derived from a CCOHTA report.\textsuperscript{17}

### 4 CLINICAL REVIEW: TERIPARATIDE

This section describes the original systematic review evaluating the clinical effectiveness of teriparatide. It also contains a summary of the CCOHTA systematic review of the bisphosphonates alendronate, etidronate, and risedronate.\textsuperscript{17}

#### 4.1 Methods

The systematic review was conducted using the Cochrane Collaboration’s methods for systematic reviews and meta-analyses.\textsuperscript{22}

##### 4.1.1 Literature search strategy

We conducted a systematic review of literature reporting on the efficacy of teriparatide in reducing osteoporotic fractures of the hip, wrist, or vertebrae. The review tried to identify all
randomized controlled trials (RCTs) of teriparatide in postmenopausal women with osteoporosis, and having a follow-up of ≥1 year for the outcome of new fractures.

Studies were identified up to March 2005 by searching several databases (Appendix 1). MEDLINE®, EMBASE®, BIOSIS Previews®, and ToxFile were searched on DIALOG®. Parallel searches were run on PubMed and The Cochrane Library. These searches were updated regularly until their discontinuation on January 7, 2006. Where possible, all searches were limited to the human population, and no language restrictions were made.

Grey literature was obtained through searching the web sites and databases of health technology assessment and related agencies. Google™ and other Internet search engines were used to search for additional web-based materials and information. These searches were supplemented by hand searching the bibliographies and abstracts of selected papers and conference proceedings, and through contacts with appropriate experts and agencies. Eli Lilly Canada, the manufacturer of teriparatide, was invited to submit information on unpublished studies.

4.1.2 Selection criteria and method

a) Study design
A RCT had to have a duration of ≥1 year.

b) Population group
The population group was postmenopausal women. Primary and secondary prevention trials were accepted. We considered that a trial focused on primary prevention if it included women whose bone mineral density (BMD) was within two standard deviations (SD) of the mean for young adult women, or if the prevalence of vertebral fracture at baseline was <20%.

c) Intervention
The intervention was teriparatide.

d) Comparators
The comparator was a bisphosphonate (alendronate, etidronate, or risedronate) or a placebo. Trials were not rejected if they included calcium or vitamin D supplements in the treatment or control arms.

e) Outcomes
The outcome was the incidence of vertebral, non-vertebral, hip, and wrist fractures.

4.1.3 Data extraction strategy

Two reviewers (AHT and DC) examined each title generated from the search, and identified potentially eligible articles, for which we obtained the abstracts. We obtained the full text of articles for abstracts that were consistent with the eligibility criteria.

Two independent reviewers (AHT and DC) abstracted all information using standardized data abstraction forms (Appendix 2). Information was abstracted on pertinent methodological aspects of the study design, participants’ characteristics, dose(s) of the drug used, the outcomes assessed (e.g., number of women with vertebral, non-vertebral, hip, and wrist fractures), and adverse events.
4.1.4 Strategy for quality assessment

Two reviewers (AHT and DC) assessed each eligible RCT for methodological quality, using the Jadad quality assessment form (Appendix 3). Studies with a Jadad score of ≥3 were assessed as higher quality. Quality assessment also included a judgment about the adequacy of allocation concealment. Research shows that studies judged to have unclear allocation concealment are more likely to be associated with biased estimates of effectiveness. The method for assigning participants to interventions should be robust against patient and clinician bias. The reviewers were required to indicate whether allocation concealment was adequate, unclear, or inadequate (Appendix 4). The internal validity of each selected trial was assessed for selection, performance, detection, and attrition bias. External validity was assessed through the evaluation of baseline population characteristics (e.g., age).

4.1.5 Data analysis methods

We calculated the relative risk (RR) of a woman experiencing a fracture if the data were available in the trials. Otherwise, we used the data regarding the number of fractures. All doses of teriparatide were included in the clinical analysis. The economic analysis only included data from women receiving the Health Canada approved dose of 20 micrograms per day.

Yearly data were calculated only if the follow-up period was ≥2 years. Pooled analyses and subgroup analyses were planned if >1 trial or subgroup was identified.

The RR of fractures based on patient-year data was also calculated. The number of fractures was used as the unit of analysis, if available. When these data were unavailable, we used the number of women sustaining a fracture. For denominators, we multiplied the number of women by the length of the study period.

4.2 Results

4.2.1 Quantity of research available

The literature search revealed 114 citations (Appendix 5 Figure 3). Eight of these articles were retrieved for further scrutiny. Six articles were excluded because there was no appropriate control group, the study was an open-label extension trial, or there were duplicate data from another trial. Two trials met all of the selection criteria.

4.2.2 Trial characteristics

The two selected trials (Appendix 6 Table 2) met the criteria for secondary prevention, and included postmenopausal women with osteoporosis who had not received treatment for their osteoporosis in the previous two to 24 months.

The study by Body et al. included women at least five years post-menopause with a lumbar spine or femoral neck BMD at least 2.5 SD below the mean for young adult women (t-score). Women were randomized to receive high dose teriparatide 40 micrograms per day injection plus oral placebo, or oral alendronate 10 mg plus placebo injection for a median duration of 14 months. Fractures of any non-vertebral site were assessed by a review of radiographs or radiologic reports.
The study by Neer et al. included women at least five years post-menopause with at least one moderate, or two mild, atraumatic vertebral fractures on radiographs of the thoracic and lumbar spine. Women with <2 moderate fractures had to have a BMD of the hip or lumbar spine that was at least one SD below the mean of premenopausal white women. Women were randomized to receive daily injections of teriparatide 20 micrograms or 40 micrograms, or placebo injection for a median duration of 21 months. New vertebral fractures were defined as a radiographic deformity (i.e., ≥20% reduction in height of a previously normal vertebra). Fractures of any non-vertebral site were assessed by a review of radiographs or radiologic reports.

The trials were of higher quality, with Jadad scores of three and four out of five. The allocation concealment was unclear for both trials. Withdrawals for any reason were 26% in Body et al. and 20% in Neer et al., as reported in the FDA medical review.

4.2.3 Data analysis and synthesis

a) Effect on fractures (secondary prevention)

A summary of fracture outcomes for the recommended 20 microgram dose of teriparatide shows the number of women with the outcome, compared with the total number of women in the sample and the patient-years at risk (calculated by multiplying number of years on treatment and sample size) (Tables 1 and 2).

No pooled estimate of RR of fracture after treatment with teriparatide was calculated, because data were available from only one trial for vertebral, hip, and wrist fractures.

<table>
<thead>
<tr>
<th>Fracture Site</th>
<th>Number of Women with Fractures (treatment/control)</th>
<th>n (treatment/control)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vertebral</td>
<td>22/64</td>
<td>444/448</td>
<td>0.35 (0.22; 0.55)</td>
</tr>
<tr>
<td>hip</td>
<td>2/4</td>
<td>541/544</td>
<td>0.50 (0.09; 2.73)</td>
</tr>
<tr>
<td>wrist</td>
<td>7/13</td>
<td>541/544</td>
<td>0.54 (0.22; 1.35)</td>
</tr>
</tbody>
</table>

*Trial results for teriparatide 40 micrograms are not reported, because the results are comparable to those of the 20 microgram dose, which is the recommended dose.
Vertebral fractures
Vertebral fractures were reported in one trial. The trial compared placebo with 20 micrograms and 40 micrograms of teriparatide given daily for a mean (SD) duration of treatment of 18 (5), 18 (6), and 17 (6) months respectively. The RR of vertebral fractures for the 20 microgram dose was 0.35 [95% confidence interval (CI): 0.22; 0.55]. This demonstrates a relative risk reduction (RRR) of 65% with teriparatide 20 micrograms and an absolute risk reduction (ARR) of 9.3% (95% CI: 5.5; 13.2). This translates into a number needed to treat (NNT) of 11 (95% CI: 8; 18), which means that 11 patients would need to be treated for 21 months (the median treatment duration) to prevent one vertebral fracture of any severity.

Hip fractures
Hip fractures were reported in one trial and occurred in a small number of patients. Findings show that, compared with placebo, teriparatide 20 micrograms has no statistically significant effect on the secondary prevention of osteoporotic hip fractures [RR: 0.50 (95% CI: 0.09; 2.73)].

Wrist fractures
Wrist fractures were reported in the same trial reporting vertebral and hip fractures. Similarly, results for the secondary prevention of wrist fracture show teriparatide 20 micrograms has no statistically significant effect compared with placebo [RR: 0.54 (95% CI: 0.22; 1.35)].

Non-vertebral fractures
Data on non-vertebral fractures (any fracture site other than vertebrae) are reported in both studies (Table 3). These data are not pooled, because the trials have different comparison groups.

When compared with placebo, teriparatide resulted in a significant effect with an RRR of 35% (RR: 0.65 [95% CI: 0.43; 0.98]) for a 20-microgram dose and 40% (RR: 0.60 [95% CI: 0.39; 0.91]) for a 40-microgram dose. Similar results were obtained for the total number of fractures. For the 20-microgram dose, the ARR was 3.4%, and the NNT was 29 (95% CI: 15; 587). This means that 29 patients would require treatment with teriparatide 20 micrograms for 21 months (the median treatment duration) to prevent a non-vertebral fracture in one patient.
Table 3: RR and numbers needed to treat for non-vertebral fractures: teriparatide versus control

<table>
<thead>
<tr>
<th>Study</th>
<th>Daily dose in micrograms</th>
<th>n</th>
<th>Number of Women with Non-vertebral Fracture</th>
<th>RR (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>teriparatide/</td>
<td>teriparatide/</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>control</td>
<td>control</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Body et al.²⁶</td>
<td>40</td>
<td>73/73</td>
<td>3/10</td>
<td>0.30 (0.09; 1.05)</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>541/544</td>
<td>34/53</td>
<td>0.65 (0.43; 0.98)</td>
<td>29 (15; 587)</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>552/544</td>
<td>32/53</td>
<td>0.60 (0.39; 0.91)</td>
<td>25 (14; 142)</td>
</tr>
<tr>
<td>Neer et al.³¹</td>
<td>20</td>
<td>541/544</td>
<td>36/62</td>
<td>0.58 (0.39; 0.87)</td>
<td>21 (12; 78)</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>552/544</td>
<td>37/62</td>
<td>0.59 (0.40; 0.87)</td>
<td>21 (12; 81)</td>
</tr>
</tbody>
</table>

Number of Non-vertebral Fractures

- Patient-year data not shown; n=sample size; CI=confidence interval; NE=not estimable with confidence; NNT=number needed to treat; RR=relative risk.

Compared with alendronate 10 mg, there was a lack of significant effect of teriparatide 40 micrograms on the number of women with a non-vertebral fracture [RR: 0.30 (95% CI: 0.09; 1.05)].²⁶

b) Additional analyses

Patient-year

When the patient-year data are used, similar results (i.e., no significant effect on hip and wrist fractures, but a significant effect on vertebral fractures) are found (Table 2).

The result for women with non-vertebral fractures in the Neer et al. study was not statistically significant [RR: 0.66 (95% CI: 0.43; 1.00)] for teriparatide 20 micrograms (data not shown).³¹

Treatment dose

Teriparatide was administered at a dose of 40 micrograms in two trials.²⁶,³¹ Based on the number of women with fractures, in the Neer et al. trial, the RR of fractures was 0.31 (95% CI: 0.19; 0.50) for vertebral fractures (data not shown), 0.74 (95% CI: 0.17; 3.29) for hip fractures (data not shown), 0.76 (95% CI: 0.34; 1.71) for wrist fractures (data not shown), and 0.60 (95% CI: 0.39, 0.91) for non-vertebral fractures (Table 3).³¹ In the Body et al. trial, the RR of non-vertebral fractures was 0.30 (95% CI: 0.09; 1.05) (Table 3).²⁶

Similar results were obtained using patient-year data (data not shown). Overall results were consistent with those for the standard 20-microgram dose.

c) Adverse events

Toxicity and withdrawals

There was no significant difference between teriparatide 20 micrograms and placebo for the risk of withdrawals due to adverse events [RR: 1.10 (95% CI: 0.69; 1.75)].³¹
At a dose of 40 micrograms, there were significantly more withdrawals due to adverse events with teriparatide compared to placebo [RR: 1.82 (95% CI: 1.21; 2.74); number needed to harm: 21 (95% CI: 12; 67)]. No significant difference was detected between teriparatide and alendronate on withdrawals due to adverse events [RR: 2 (95% CI: 0.86; 4.67)].

Data for withdrawals due to any reason were not reported by Neer et al., but are reported in the FDA Medical Review as approximately 20% with no significant differences between teriparatide and placebo groups. Withdrawals due to any reason were not different in the study comparing teriparatide and alendronate [RR: 1.38 (95% CI: 0.79; 2.40)]. Adverse events reported in the trials were generally mild, and led to withdrawals rather than long-term detriment to quality of life.

### 4.3 Systematic Review of Bisphosphonates

The systematic review by Wells et al. shows that the main benefit of the bisphosphonates, relative to placebo, lies in the secondary prevention of fractures (Appendix 6 Table 3).

For etidronate, eight secondary prevention and three primary prevention trials were found. Etidronate’s main benefit is in the secondary prevention of vertebral fractures. There were no statistically significant reductions in vertebral fractures when used for primary prevention. For primary or secondary prevention, no statistically significant reductions in non-vertebral, hip, or wrist fractures were observed. These 11 trials indicate that adverse event rates were similar between etidronate and placebo. Data available also indicate that there were no statistically significant differences between etidronate and placebo in terms of discontinuations due to adverse events, or overall drop-outs.

For alendronate, eight secondary prevention and three primary prevention trials were found. Alendronate’s main benefit is in the secondary prevention of all osteoporotic fractures. At a dose of 10 mg per day, statistically significant reductions in vertebral, non-vertebral, hip, and wrist fractures were observed. With the exception of vertebral fractures, there were no statistically significant reductions found for the primary prevention of osteoporotic fractures. These 11 trials indicate a similar rate of adverse events for alendronate and placebo. Available data also indicate there were no statistically significant differences between alendronate and placebo in terms of discontinuations due to adverse events, or overall drop-outs.

Five risedronate secondary prevention trials and one primary prevention trial were found. Risedronate’s main benefit lies in the secondary prevention of most osteoporotic fractures. At a dose of 5 mg per day, statistically significant reductions are observed in vertebral, non-vertebral, and hip fractures, but not in wrist fractures. The risk for primary prevention was impossible to estimate because of a lack of data. These six trials indicate a similar rate of adverse events for risedronate and placebo. Available data indicate that there were no statistically significant differences between risedronate and placebo in terms of discontinuations due to adverse events, or overall drop-outs.

### 4.4 Discussion

The efficacy results of the systematic review of bisphosphonates, and of teriparatide in the treatment of osteoporosis in postmenopausal women are summarized in Appendix 6 Table 3. There is a scarcity of evidence available for teriparatide, with two published RCTs meeting our
eligibility criteria, both for the secondary prevention of osteoporotic fractures. The ability to generalize the findings may be limited by the population studied (e.g., in both trials, most patients had no prior exposure to osteoporosis therapies). The one trial\(^2\) of teriparatide versus an active comparison (alendronate) only included 146 participants. The quality assessment in both trials revealed potential sources of bias, such as unclear allocation concealment. One study\(^3\) indicates that, compared with placebo, teriparatide reduces the risk of vertebral and non-vertebral fractures in women at a high risk of fractures. No statistically significant effect could be identified specifically for hip and wrist fractures, probably because of sample size. One study\(^2\) also compared teriparatide 40 micrograms to alendronate. It reported no difference in the rate of non-vertebral fractures between the two agents. No comparative trials with other bisphosphonates were identified. More research is required to better determine the comparative effectiveness of teriparatide versus all bisphosphonates.

Evidence from the CADTH review of bisphosphonates indicates that the main benefits of bisphosphonate therapy relative to placebo lie in the secondary prevention of osteoporotic fractures (i.e., the prevention of fractures in patients with a BMD 2 SD below the peak bone mass or with pre-existing osteoporotic fractures).\(^1\) The magnitude of this effect varies among bisphosphonates.\(^1\) Eleven trials evaluated etidronate, and reported that the use of etidronate is associated with a 47% reduction in vertebral fractures. Most trials enrolled a small number of participants (mean of 113 patients per trial), and were not necessarily designed to measure fractures, limiting this finding. The available evidence for alendronate and risedronate is more robust. For risedronate, six RCTs were published, with a total of 13,795 participants. Based on these trials, risedronate led to a 39% reduction in vertebral fractures, a 26% reduction in hip fractures, and a 20% reduction in non-vertebral fractures. In comparison, 11 RCTs that enrolled a total of 12,099 participants evaluated alendronate. Based on these trials, alendronate was associated with reductions in vertebral (45%), non-vertebral (23%), hip (53%), and wrist (48%) fractures; although statistical significance was only reached for wrist fractures in the yearly fixed-effect analysis.\(^1\)

These differences may explain partly the current uptake by prescribers, with alendronate (most effective) dominating the market. The 2004 Canadian market shares of these drugs, based on utilization data provided by IMS Health Canada, were alendronate (51%), risedronate (29%), and etidronate (20%).

## 5 ECONOMIC ANALYSIS

### 5.1 Review of Economic Studies

#### 5.1.1 Methods

We reviewed economic evaluations of osteoporosis treatments for postmenopausal women. Studies focusing on hormone replacement therapy (HRT) were excluded, because the role of this therapy in the management of osteoporosis has diminished.\(^3\) Using an electronic search in MEDLINE, EconLit, and Current Contents, we identified studies from January 1990 to May 2004, using the keywords: cost-benefit analysis, cost, cost analysis, osteoporosis, and fractures. This was supplemented by searching the reference list of relevant studies, and by searching the Internet. Studies were also identified from previously published review articles.\(^3\)
Relevant studies were identified, and data were extracted by one reviewer (DC) on country of origin, treatment comparators, study design (type of model or clinical trial), patient characteristics, form of analysis (cost minimization, cost effectiveness, or cost utility), outcome measure, summary of results, and conclusions. Each study was assessed for quality in terms of how they compared with the recommendations described in Appendix 6 Table 4.

5.1.2 Study results

Appendix 6 Table 5 summarizes all the identified economic evaluations of therapies for osteoporosis. Five studies were identified from the UK,38-42 three from Canada,18,43,44 two each from Sweden45,46 and Denmark,47,48 and one each from the US,49 Italy,50 and Norway.51 Eight studies were cost-utility analyses; the other seven were cost effectiveness analyses with hip fractures (4), vertebral fractures (2), and risk ratios (1) as outcome measures. Studies were published from 1994 to 2003; seven were published before 2000.

Of the 15 studies, 12 included at least one bisphosphonate as a comparator; nine included alendronate; two included risedronate; and six included etidronate. The conclusions of the studies including bisphosphonates were inconsistent. Five studies compared alendronate with etidronate. Two found that etidronate was more cost-effective;18,38 two other studies found alendronate to be more cost effective.44,50 It was difficult to derive any meaningful interpretation from the remaining study, because its focus was to demonstrate a particular method of analysis, and it used mainly hypothetical data.51 Both risedronate studies found that the drug was cost-effective. In one Canadian study, risedronate was dominant over alendronate, and had an incremental cost-utility ratio (ICUR) that may be considered to be acceptable to decision makers when compared with no drug therapy.43 In a UK study, risedronate was found to be dominant over no drug therapy.41 Both studies had shortcomings related to the methods used for modelling fractures with or without therapy.

Three studies did not include a bisphosphonate as a comparator; they focused on calcium with or without vitamin D.42,46,49 In all three studies, calcium was found to be effective and cost saving.

5.1.3 Study quality

When drawing conclusions from the published studies, it is necessary to consider that the overall quality of studies was poor when assessed against the 15 recommendations for good practice (Appendix 6 Table 6). The study of highest quality was the UK National Health Service health technology assessment report on osteoporotic treatments40 (Appendix 6 Table 6). It met 13 of the 15 standards,40 but it failed to provide explicit head-to-head comparisons between therapies, and to model discontinuation rates based on actual data.40 Other studies met from one to 11 standards. One study adequately allowed for drug discontinuation.44 Other recommendations that were rarely met were adequate modelling for fractures (three studies), modelling of head-to-head comparisons (three), and incorporation of benefit beyond therapy (three). Based on the quality of these studies, we cannot derive enough evidence regarding the cost effectiveness of bisphosphonates in Canada.
5.2 Primary Economic Evaluation

5.2.1 Methods

a) Model structure

We used a decision-analytic model that reflects the natural history of women with osteoporosis. It incorporates the sequelae associated with osteoporosis (e.g., fracture), and the transition of women in terms of the development of osteoporosis, history of fracture, and residential status (Appendix 5 Figure 4). We used the most recently available data relevant to the Canadian population. After considering the chronic nature of osteoporosis, we chose a Markov model with a one-year cycle length and a lifetime horizon.

We assumed that the probability of a woman experiencing a hip, wrist, or vertebral fracture depends on age, osteoporotic status, and previous history of osteoporotic fractures. Hip and vertebral fractures are associated with excess mortality; hip fractures are also associated with increased admission to LTC facilities. The probability of hip fracture and the mortality after a hip fracture increase if a woman lives in LTC facilities.

For our analysis, we needed to distinguish between women on the basis of fracture history, and whether they live in the community or in LTC facilities. Based on this, there will be different age-specific transition probabilities for fracture (hip, wrist, and vertebral), and associated risks of mortality from fracture (hip and vertebral only). For all states, there is an associated transition probability to death. This varies by a woman’s age and the incidence of fracture; the model incorporates a higher risk of mortality after hip or vertebral fracture.

The model was populated with relevant transition probabilities, and estimates of the costs and utilities associated with each health state (Appendix 6 Tables 7 to 9). Input parameters estimated through sample information, rather than population estimates, were represented by a probability-density function, based on their expected values and the associated uncertainty. The probability-density functions represent the likelihood of alternative population estimates for the parameters of interest. Drug prices and input values obtained from population, rather than sample data, were assumed to be fixed.

The model was developed using a Microsoft® Excel® 2000 spreadsheet incorporating the Crystal Ball® software enhancement to facilitate Monte Carlo simulation (MCS). The MCS involves obtaining several outcome estimates, by rerunning the model and using different values for each data input, randomly selected from that variable’s probability-density function.

b) Transition probabilities

Introduction
The following age-specific transition probabilities were required to simulate progression through the model:

- probability of developing osteoporosis
- probability of being admitted to a LTC facility
- probability of hip, wrist, and vertebral fracture specific to residential status, osteoporotic history, and treatment
- probability of mortality with or without fracture.
In some cases, the required data were unavailable. Alternative data parameters, however, are available. These allow the computation of the necessary parameters through calibration of the model.\(^5^9\) For example, in the model, age-specific rates of hip fractures for community-dwelling women were required for women not diagnosed with osteoporosis, women diagnosed with osteoporosis but without previous osteoporotic fracture, and women with previous osteoporotic fracture. The underlying age-specific rate of hip fracture in the community was known. The RR of fracture for women with osteoporosis compared to those without osteoporosis, and the RR of fracture for osteoporotic women given a previous osteoporotic fracture versus no previous fracture were known. If the analysis was conducted by weighting the underlying rate by the two RRs, this would lead to an overestimate of the rate of fracture in the community (Appendix 5 Figure 5). As a result, we needed to calibrate the model.

Calibration involves adjusting the estimates, so the available population data can be reproduced. Failure to adjust the underlying rates of fracture would bias results in favour of active treatment, because the underlying rates would be overestimated, and lead to an overestimate in the number of fractures avoided, and their consequent costs and outcomes.

**Probability of developing osteoporosis**
The Canadian Multicentre Osteoporosis Study (CaMos) has reported the prevalence of osteoporosis by age in the Canadian population.\(^6^0\) Prevalence for the age ranges 40 to 49, 50 to 59, 60 to 69, 70 to 79, 80+ were 1.3%, 6.0%, 18.2%, 27.0%, and 42.1%. Using these data, it is possible to calibrate the model by adopting transition rates that can replicate the prevalence rates obtained from the CaMos study.

**Probability of admission to an LTC facility**
Age-specific transition rates for admission to an LTC facility for women after an occurrence of hip fracture were obtained from a study of patients in Edmonton.\(^5^5\) The analysis was based on 338 patients who lived in the community before fracture and who survived the immediate period post-fracture. The rates of admission to an LTC facility after fracture for patients aged 65 to 74, 75 to 84, and 85+ were 5.6% (n=90), 16.6% (n=157), and 29.8% (n=184) respectively. Probability-density functions for these variables assume a beta distribution based on the number of patients in each age cohort.

Estimates of the probability of living in an LTC facility (i.e., prevalence) are available for the fiscal year 1993-1994, based on data from Statistics Canada.\(^5^6\) For age groups 65 to 69, 70 to 74, 75 to 79, 80 to 84, and 85+, the probabilities of living in an LTC facility were 0.68%, 1.57%, 4.19%, 10.71%, and 29.93%. The model is calibrated by adopting transition rates that make it possible to replicate the probabilities of living in an LTC facility.

**Probability of fracture**
The probabilities of hip fracture for women living in the community and in LTC facilities were estimated for the fiscal year 1993-1994 with data from the Canadian Institute of Health Information, and Statistics Canada.\(^6\),\(^5^6\) Age-specific probabilities that were estimated through a regression analysis confirmed an exponential increase with age. The age-specific risk of fracture per 100,000 community-dwelling women was derived from the formula \(0.578 \times e^{0.096 \times \text{age}}\). For women living in an LTC facility, the age-specific risk was higher, and derived from the formula \(73.99 \times e^{0.049 \times \text{age}}\).
Vertebral fracture rates were based on data from the Manitoba Health Services Insurance Plan for 1981 to 1984. The study used data to derive age-specific estimates for the rate of vertebral fracture. The study incorporated the ambulatory and hospital care of vertebral fractures. The annual rates of vertebral fracture per 100,000 women, aged 50 to 59, 60 to 69, 70 to 79, and 80+, were 54.3, 89.9, 192, and 438.3 respectively.

It was necessary to adjust the fracture rates in the model to estimate the age-specific risk for women based on their osteoporotic status. From a meta-analysis of prospective cohort studies, the RR of fracture was 1.5 for one SD decrease in BMD, based on the distribution of BMD for young healthy adult women. Assuming the BMD for Canadian women with osteoporosis is on average 1.45 SD below that of non-osteoporotic women, the RR of fracture, based on the prevalence of osteoporosis, is estimated as 1.8 (i.e., 1.51.45). From an analysis of the fracture rates in the placebo groups of the Fracture Intervention Trial, the RR of fracture for a woman with osteoporosis and with a previous fracture is 1.32.

Mortality rates

The mortality rates for Canadian women immediately after a hip fracture were obtained from the same study that provided the probability of hip fracture. The age-specific mortality rates per 100,000 community-dwelling women after fracture were derived from the formula 0.010 x e0.084 x age. For women living in LTC facilities, the formula is 0.056 x e0.072 x age.

Canadian mortality rates immediately after a vertebral fracture were unavailable. We used the results from a US prospective cohort study of 9,704 women aged >65 in the model. In this study, the RR of mortality a year after a vertebral fracture was 1.16.

Age-specific all-cause mortality rates were used in the model for a hip or vertebral fracture after one year post-fracture.

Canadian age-specific all-cause mortality rates for women are available from 1990 to 1992. The model was calibrated by adopting age-specific mortality rates for women without fracture, allowing us to replicate the age-specific all-cause mortality rates for the Canadian population of women, given the effect of hip and vertebral fractures on mortality and their respective incidences.

c) Costs

Introduction

Costs for each state in the decision model were estimated and adjusted to 2003-2004 Canadian dollars. The model adopts the perspective of the health and social care system — the costs of health, social services, and LTC are included. The analysis approximates results from a societal perspective, because the productivity losses associated with informal care after a fracture are shown to be minimal because of the patients’ advanced age.
**Hip fractures**
The health care resource costs associated with the treatment of a hip fracture in the first year comprise immediate acute care, rehabilitation, and institutionalization. Costs associated with hip fracture beyond the first year post-fracture are discussed here.

Estimates were based on a study of the costs of hip fracture for 504 patients in Hamilton ON. Costs for individual patients were estimated from a review of hospital records linked with data from community services and LTC facilities. The coefficients from a multivariate analysis are used to estimate the mean costs for each group of survivors after a hip fracture. The cost for patients whose deaths are attributable to fracture is assumed to be the same for all age groups — C$15,498.

The probability density function for the cost of hip fractures is assumed to take a normal distribution with the standard error of the mean for each group, based on the SD for all survivors, and adjusted by the sample in each group. For deaths after a hip fracture, the function is based on the actual mean and standard error for this group.

**Vertebral fractures**
For women with vertebral fracture, the proportion requiring hospitalization varies by age: 40%, 30%, 38%, and 45% for ages 50 to 59, 60 to 69, 70 to 79, and 80+ respectively.

The costs per in-patient stay for women with vertebral fractures were obtained from an analysis of data provided by the Ontario Case Costing project for one teaching hospital and seven community hospitals. The mean cost per hospitalized fracture patient was C$4,646, inflated to 2004 Canadian dollars. The cost of treating vertebral fractures on an ambulatory basis is estimated to be C$128, based on the estimated resource use obtained from a survey of Canadian physicians.

The probability density functions for the costs of a vertebral fracture treated in hospital or treated on an outpatient basis were assumed to be normal distributions, with an assumption of a standard error of the mean equivalent to 25% of the expected value.

**Wrist fractures**
Wrist fractures are assumed to be exclusively treated on an ambulatory basis. The cost of treating wrist fractures was estimated to be C$275, calculated on the same basis as vertebral fractures from a survey of Canadian physicians. The probability density function was assumed to be a normal distribution with a standard error of the mean equivalent to 25% of the expected value.

**LTC**
The annual cost of LTC is assumed to be the difference between the annual costs after hip fracture for those staying in the community and for those admitted to LTC facilities (C$21,335). The model only incorporates the incremental costs of LTC occurring after a hip fracture. Although a patient may be admitted to an LTC facility, the full stay may not be attributable to hip fractures, because the patient may have been admitted over time for other causes. We assume that the proportion of an LTC stay attributable to fracture is unknown, with a mean of 0.5 (beta 1,1) where zero means only the first year post-fracture is attributable, and one means the rest of the LTC stay is attributable.
Utilities
Utility values were required for normal health, hip fracture, wrist fracture, and vertebral fracture. These values were adjusted to allow for the decline in utility with age.

Consistent with the need to use data that are specific to the Canadian context, utility values were derived from the most recent well designed Canadian study. The values for normal health and fractures were estimated through communication with a sample of postmenopausal women. Preference scores for all health states were obtained by using a visual analogue scale. Preference scores and utility values were obtained for the women’s current health by using a visual analogue scale and the standard gamble approach. Preference scores were transformed into utility values by assuming a power function relationship. The power function relationship was based on the data relating to current health.

Health states describe the acute effects of fracture; thus, it is necessary to allow for improvements in health status over time. Utility values for spine and wrist fractures are assumed to improve linearly, so that the individual will be restored to normal health for their age group by the year’s end. The total disutility from spine and wrist fractures will be half the difference between the utility value for normal health and fracture. For hip fracture, utility is assumed to improve linearly, so the individual will be restored to normal health for their age group by the end of the second year.

Utility decline by age is incorporated using data for women from the Canadian National Population Health Survey. The average age of respondents to the osteoporosis utility exercise was 55 to 59. The utilities for fracture states were converted to age-specific utilities as in the following example:

\[
Utility_{spine\ fracture\ aged\ 70\ to\ 74} = \frac{Utility_{55\ to\ 59}^{70\ to\ 74}}{Utility_{55\ to\ 59}} \times Utility_{spine\ fracture} \\
= \frac{0.83}{0.86} \times 0.77 = 0.74
\]

The uncertainty of utility values in the model is represented by a normal distribution with mean and standard errors derived from the utility elicitation exercise.

d) Treatment specific parameters
Data requirements
To facilitate the economic evaluation of treatment interventions, the model requires estimates of the following parameters for each therapy:
- fracture-specific RRR during therapy
- benefit beyond therapy duration
- continuation rate for therapy
- monthly treatment costs.

Effect of therapy on risk fractures
The economic evaluation focused on the secondary prevention of osteoporotic fractures, because of the scarcity of clinical effectiveness data to support primary prevention with teriparatide or the bisphosphonates.
The effect of bisphosphonates on the risk of fractures was derived from a CADTH meta-analysis of clinical RCTs. The meta-analysis included RCTs of ≥1 year duration.17

We focused our analysis on identifying the proportional risk reduction attributable to therapy for hip, wrist, and vertebral fractures in women with a previous fracture. The economic analysis uses data from the trials identified in the systematic review, although the effect of bisphosphonates is measured differently in the economic analysis. First, the analysis needs to focus on the decrease in the number of fractures rather than the number of women experiencing a fracture. Second, the analysis needs to distinguish between wrist and hip fractures, rather than focus on non-vertebral fractures in general. Third, the model adjusts for actual compliance with therapy (rather than compliance during a trial). The RRR needs to relate to number of years of therapy (patient-year at risk), and not number of years in the trial. Each trial was reviewed, and data were extracted based on the number of fractures and total years of therapy. Similar data were then obtained for teriparatide (Appendix 6 Table 10).

The analysis assumes indirect RRs, based on the ratio of RRs from the placebo-controlled trials. Appendix 6 Table 11 shows the assumed RRs of hip fracture between therapies and their 95% CIs. A sensitivity analysis was conducted using RRs based on the number of women with fractures.

Benefit of therapy beyond therapy duration
Evidence shows that patients experience continued reductions in the risk of fracture after stopping therapy; although the follow-up of patients has lasted <2 years after treatment curtailment.73,74 This analysis follows previous studies by assuming a linear reduction of benefit after the curtailment of therapy for all bisphosphonates; though this benefit is restricted to <2 years.

To incorporate uncertainty about the decline of benefit after treatment, the rate of decline of benefit was modelled as an exponential function, where zero represents a linear benefit, $-\infty$ represents no decline over the two years, and $+\infty$ represents no benefit post-curtailment. This can be expressed by the formula:

$$RR_{fracture} = \left(3 - \frac{T_{Stop}}{3}\right)^{3} RR_{treatment}$$

$T_{stop}=$years since curtailment of therapy; $RR_{fracture}=$relative risk of fracture; $RR_{treatment}=$relative risk of fracture while on therapy; $r=$rate of decline of benefit after curtailment ($r=0$ for linear reduction in benefit; $r=+\infty$ if no decline in benefit over two years; $r=-\infty$ if no benefit post-treatment curtailment); $\infty=$infinity.

Uncertainty about the rate of decline of benefit was characterized by a normal distribution (mean=0; standard error=1). The extremes associated with the distribution correspond to two scenarios suggested by the WHO Collaborating Centre 75 that all benefit is lost immediately after stopping therapy, or that the relative risk of fracture remains as estimated in the trial.

Continuation with therapy
The retention rates for bisphosphonates were estimated using data from the Ontario Drug Benefit Scheme. Data related to claimants who had not taken the drug before, between July 1999 and June 2001. One-year retention rates were obtained for each drug based on the proportion of claimants who continued on therapy after one year. The rates for alendronate, risedronate, and etidronate were 65%,
62%, and 57% respectively. Given the similar retention rates and the predominance of prescriptions for etidronate, we adopted the same retention rate of 57% for all treatments in our analysis.

Continuation with therapy is assumed to decline yearly, based on the observed retention rate. Duration is assumed to be no more than seven years, in line with the maximum follow-up of patients in clinical trials. The proportion of patients who are likely to be continuing with therapy at seven years will be approximately 2%.

Despite the large sample sizes (n=115,426) used to estimate retention rates, uncertainty is assumed to be high, because the observed data relate to the first 12 months in therapy. To reflect the uncertainty about long-term continuation with therapy more accurately, we used a beta distribution with a presumed sample size of 100. There is a lack of data on the long-term compliance with therapy for teriparatide. For the base analysis, it is assumed that the compliance will be the same as that of bisphosphonates (57% retention rate per year with a maximum duration of therapy of 18 months). For the sensitivity analysis, it is assumed that there is full compliance for 18 months (the recommended duration for use).

To estimate the incremental effects of individual therapies, switching between therapies was not permitted in the model.

**Costs of therapy**
We found the costs of alendronate, etidronate, and risedronate by reviewing data from a selection of provincial drug formularies. The median price across the formularies was used in this analysis; the minimum and maximum prices were used in the sensitivity analyses (Appendix 6 Tables 1 and 12). A C$10 professional charge was added per three-month prescription. We obtained the wholesale cost for teriparatide from PPS Pharma.

The yearly cost of alendronate was estimated at C$706.79, based on a dosage of 10 mg once daily. The yearly cost of etidronate based on a dosage of 200 mg twice daily for 14 days in a three-month cycle was estimated at C$191.41. The yearly cost of risedronate based on a dosage of 5 mg once daily was estimated at C$654.67. The yearly cost of teriparatide, based on a dosage of 20 micrograms per day, was estimated at C$9,713.06. We assumed fixed costs for drug therapies.

e) **Analytical framework**

**Base analysis**
The model allowed us to conduct a cost-utility analysis where outcomes were expressed in quality-adjusted life-years (QALYs). Analysis is presented in terms of the incremental cost per outcome gained.

We conducted our analysis from the perspective of a provincial ministry of health and followed CCOHTA’s *Guidelines for the economic evaluation of pharmaceuticals: Canada*. For the base case analysis, the costs and benefits were discounted at 5% per annum. The sensitivity analyses were conducted using discounts of 0% and 3%.

**Analysis of variability**
The base analysis is presented for an 80-year-old woman with a previous osteoporotic fracture. Further analyses are conducted for a 65-, 70-, and 90-year-old woman with a previous fracture.
Analysis of uncertainty
We conducted a sensitivity analysis to assess the robustness of the study’s results to changing assumptions in the model:

- assuming full compliance with teriparatide for 18 months
- assuming no benefit beyond therapy curtailment
- adopting discount rates of 0% and 3%
- focusing on patients with a higher risk of fracture (assuming an RR of fracture=2 or =4 compared with the base case population of women with previous osteoporotic fractures)
- using lowest and highest annual drug costs
- basing RR on the number of women with fractures.

The base analysis was conducted using a deterministic analysis and following CCOHTA guidelines, whereby point estimates for each parameter were entered in the model, and an estimate of the cost effectiveness of treatment was obtained. A probabilistic analysis was conducted using MCS. The relationship between input parameters and outcomes can be non-linear, so the expected values of outcomes obtained from an MCS can differ from those of the deterministic analysis. An analysis based on MCS avoids the potential for non-optimal decisions, which can occur with deterministic analyses, and allows an assessment of contribution to uncertainty over outcomes from specific data parameters.

We used the Crystal Ball® software enhancement for Microsoft Excel® software for this MCS analysis. Probability distributions were specified for relevant parameters and different estimates of outcomes, such as costs and time with response. QALYs were obtained by re-running the model, using values for each data input randomly selected from that variable’s probability distribution. In this study, 3,000 replications were conducted; i.e., a set of 3,000 outcome estimates were obtained.

For the MCS, outcomes were expressed as means with uncertainty depicted by a 95% credible interval that is the 2.5th and 97.5th percentile of the distribution of outcomes. For economic analyses relating to public sector decision making, the statistic of most interest regarding optimal decision making should be the expected value (or mean) of the outcome. The cost effectiveness of treatment is presented in terms of the incremental cost per QALY gained (the ratio of the mean incremental costs and incremental QALYs) and not the mean ratio.

Cost effectiveness acceptability curves (CEACs) are supplied for the baseline patient scenario (80-year-old women with a previous fracture). In a CEAC, the probability that a particular therapy is optimal (i.e., net monetary benefit for a therapy is positive in all comparisons) is depicted for each potential value of λ (the threshold value for a QALY).

5.2.2 Results

a) Base analysis
Table 4 provides estimates of the costs and QALYs associated with each treatment strategy for an 80-year-old woman with a previous fracture. Alendronate is shown to be the most cost-effective treatment. Risedronate and teriparatide are shown to be dominated by alendronate; etidronate is dominated by no drug therapy (Appendix 5 Figure 6). The incremental cost effectiveness ratio (ICER) for alendronate compared with no drug therapy is C$13,000. If the willingness to pay is <C$13,000 per QALY, no drug therapy is optimal; if the willingness to pay is >C$13,000 per QALY, alendronate is optimal.
b) Analysis of variability
Tables 4 and 5 present similar results for women who are 65, 70, or 90 years old. In each scenario, similar findings to the base analysis are found (no drug therapy or alendronate were cost-effective). The relative cost effectiveness of alendronate increases with age as the baseline risk of fracture rises.

c) Analysis of uncertainty
Appendix 6 Table 13 shows the results of the univariate sensitivity analysis, which demonstrates that results are robust to significant changes in parameters.

The MCS found similar results to the preceding base analysis (Appendix 6 Table 14). For an 80-year-old woman with previous fracture, teriparatide, risedronate, and etidronate were subject to dominance. The ICER for alendronate compared with no drug therapy is C$11,000.

Alendronate is the most likely therapy to be cost-effective for all threshold values of a QALY ($\lambda$) between C$20,000 and C$100,000 (Appendix 5 Figure 7). Teriparatide had a 0% chance of being the most cost-effective for all values of $\lambda$.

5.2.3 Discussion

Using data from disparate sources poses a problem when using decision analysis to make economic evaluations. We faced this issue in our study. We used Canadian data in almost all instances of the analysis; therefore, it can be argued that it is valid in the Canadian context. We used a sensitivity analysis to test some assumptions explicitly, and addressed the inherent uncertainty of sample information using a probabilistic analysis.

Base analyses and subsequent sensitivity analyses found consistent results, demonstrating that two treatment options had the potential to be cost-effective. Whether alendronate or no drug therapy was more cost-effective was influenced by age, because the risk of fracture rises exponentially with age. For younger women, the threshold value by which alendronate is preferred to no drug therapy is higher than for older women. For all scenarios, teriparatide is more effective than etidronate or risedronate, but more costly than other treatment options.

The probabilistic analysis showed that the uncertainty, relative to determining the most cost-effective treatment option, was influenced by several factors, including the willingness to pay, the uncertainty relating to the effectiveness of etidronate, and the lack of data about the effectiveness of teriparatide. Despite this inherent uncertainty, the probability that teriparatide was the most cost-effective treatment option was zero for all threshold values.

We used an indirect comparison to compare teriparatide to bisphosphonates for the secondary prevention of osteoporotic fractures. This approach was required because of the lack of direct comparative effectiveness data. Efficacy data on teriparatide versus placebo were limited to one RCT.
### Table 4: Lifetime costs and QALYs associated with alternative treatment options

<table>
<thead>
<tr>
<th>Costs (C$)</th>
<th>QALYs</th>
<th>Incremental Cost per QALY Gained versus No Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-year-old Woman with Previous Fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>etidronate</td>
<td>$13,300</td>
<td>18.813</td>
</tr>
<tr>
<td>no drug therapy</td>
<td>$12,700</td>
<td>18.814</td>
</tr>
<tr>
<td>risedronate</td>
<td>$14,200</td>
<td>18.819</td>
</tr>
<tr>
<td>alendronate</td>
<td>$14,200</td>
<td>18.823</td>
</tr>
<tr>
<td>teriparatide</td>
<td>$37,700</td>
<td>18.823</td>
</tr>
<tr>
<td>70-year-old Woman with Previous Fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>etidronate</td>
<td>$12,200</td>
<td>12.205</td>
</tr>
<tr>
<td>no drug therapy</td>
<td>$11,600</td>
<td>12.207</td>
</tr>
<tr>
<td>risedronate</td>
<td>$12,800</td>
<td>12.213</td>
</tr>
<tr>
<td>alendronate</td>
<td>$12,700</td>
<td>12.218</td>
</tr>
<tr>
<td>teriparatide</td>
<td>$32,400</td>
<td>12.218</td>
</tr>
<tr>
<td>80-year-old Woman with Previous Fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>etidronate</td>
<td>$9,200</td>
<td>4.280</td>
</tr>
<tr>
<td>no drug therapy</td>
<td>$8,700</td>
<td>4.283</td>
</tr>
<tr>
<td>risedronate</td>
<td>$9,200</td>
<td>4.291</td>
</tr>
<tr>
<td>alendronate</td>
<td>$8,900</td>
<td>4.300</td>
</tr>
<tr>
<td>teriparatide</td>
<td>$22,700</td>
<td>4.299</td>
</tr>
<tr>
<td>90-year-old Woman with Previous Fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>etidronate</td>
<td>$5,800</td>
<td>1.428</td>
</tr>
<tr>
<td>no drug therapy</td>
<td>$5,500</td>
<td>1.422</td>
</tr>
<tr>
<td>risedronate</td>
<td>$5,500</td>
<td>1.443</td>
</tr>
<tr>
<td>alendronate</td>
<td>$5,000</td>
<td>1.453</td>
</tr>
<tr>
<td>teriparatide</td>
<td>$14,400</td>
<td>1.452</td>
</tr>
</tbody>
</table>

A treatment is dominated by another, if it is more costly and less effective; i.e., no matter what the willingness to pay for a health outcome, the treatment will not be cost-effective. A treatment dominates another, if it is less costly and more effective. QALY=quality-adjusted life-years.

### Table 5: Results for Women with Previous Fracture

<table>
<thead>
<tr>
<th>65-year-old</th>
<th>etidronate, risedronate, and teriparatide dominated by alendronate; no drug therapy cost-effective if λ&lt; C$169,600; alendronate cost-effective if λ&gt; C$169,600</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-year-old</td>
<td>etidronate, risedronate, and teriparatide dominated by alendronate; no drug therapy cost-effective if λ&lt; C$97,200; alendronate cost-effective if λ&gt; C$97,200</td>
</tr>
<tr>
<td>80-year-old</td>
<td>etidronate, risedronate, and teriparatide dominated by alendronate; no drug therapy cost-effective if λ&lt; C$13,000; alendronate cost-effective if λ&gt; C$13,000</td>
</tr>
<tr>
<td>90-year-old</td>
<td>etidronate, teriparatide, no drug therapy, and risedronate dominated by alendronate</td>
</tr>
</tbody>
</table>

λ=willingness to pay
Acknowledging these limitations, it may be implied that teriparatide is potentially more effective than other treatment options (Appendix 6 Table 11). Given its cost, it is not considered to be cost-effective by conventional terms. Despite further sensitivity analyses, increasing the baseline risk of fracture, the ICER for teriparatide remained unattractive. Two further analyses can highlight this issue. First, consider if teriparatide was 100% successful in the prevention of fracture i.e., for the period of treatment, a patient had zero risk of fracture, and that this benefit would decline after the curtailment of treatment. In this scenario, for a woman aged 80 years with a previous fracture, the incremental cost per QALY gained for teriparatide compared with alendronate is C$911,000. Even if teriparatide is maximally effective, it is unlikely to be cost-effective.

A second analysis can address the issue of whether teriparatide can be cost-effective if it is targeted at high risk groups. Consider the unlikely scenario that we know which patients will fracture their hip in the upcoming year if they do not receive treatment. For a population of 100 such patients, it is assumed that teriparatide would lead to the avoidance of 51 hip fractures. Alendronate would still be more effective in leading to the avoidance of 53 hip fractures. Even if teriparatide can be targeted at the highest risk groups, it would still be dominated by alendronate. The analysis comparing teriparatide and the bisphosphonates is possible only by indirect comparisons based on placebo-controlled trials. Given the lack of head-to-head clinical trials, it could be decided that we should consider only the direct comparisons available in trials, i.e., each therapy could only be compared with no drug therapy. This restrictive analysis would fail to provide adequate information to help decision makers in resource allocation decisions. The analysis requires us to imply a RRR between treatments. For example, based on the relative efficacy of teriparatide compared with no drug therapy (RR=0.51), and risedronate compared with no drug therapy (RR=0.73), the implied RR of hip fracture for teriparatide compared with risedronate is 0.69 with a wide 95% CI (0.12, 3.79).

The analysis is based on the daily dosages for risedronate and alendronate, because this is what the RCTs are based on. Both therapies are commonly prescribed using a less expensive, once-a-week formulation. If we assume that each therapy is equally effective when administered once a week as it is when administered daily, the relative cost effectiveness of both therapies improves significantly, and the relative cost effectiveness of teriparatide becomes significantly worse. A significant factor affecting the cost effectiveness of osteoporotic medications is their relative price.

6 HEALTH SERVICES IMPACT

6.1 Population Impact

Osteoporosis affects approximately 30% of postmenopausal women, and increases in prevalence with age.3,4,60 It is estimated that the number of Canadian women with osteoporosis will grow from 686,000 in 2004 to 805,000 in 2011. An estimated 29,000 hip fractures will occur among Canadian women in 2011, up from 24,500 in 2004 (Table 6).
Table 6: Canadian women ≥65 years old, and number with osteoporosis or hip fracture

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2006</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of females ≥65</td>
<td>2,345,500</td>
<td>2,457,300</td>
<td>2,740,600</td>
</tr>
<tr>
<td>years or older</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated number with</td>
<td>685,743</td>
<td>726,611</td>
<td>805,225</td>
</tr>
<tr>
<td>osteoporosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated number of</td>
<td>24,498</td>
<td>26,338</td>
<td>29,170</td>
</tr>
<tr>
<td>hip fractures</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Population data: Statistics Canada;82-84 prevalence of osteoporosis: Tenenhouse et al.;60 incidence of hip fracture: Papadimitropoulos et al.5

Bisphosphonates are prescribed widely in Canada for osteoporosis. In 2004, approximately five million prescriptions for bisphosphonates were filled. Between 1999 and 2004, bisphosphonates sales increased from C$99 million to C$312.2 million, a growth rate of >200%. In 2004, the proportion of total sales for etidronate, alendronate, and risedronate were 20%, 50%, and 30% respectively. Appendix 5 Figures 1 and 2 shows the number of prescriptions and total sales of oral bisphosphonates in Canada.

Table 7 summarizes the Canadian publicly funded drug plan listings of bisphosphonates and teriparatide. Etidronate with calcium is available in most formularies as a regular benefit, while alendronate and risedronate are available in most jurisdictions as a restricted or exceptional status benefit. Teriparatide was not listed on any Canadian jurisdiction formulary as of August 2005. In Canada, teriparatide is indicated for the treatment of postmenopausal women with severe osteoporosis who are at high risk of fracture, or who have failed or are intolerant to previous osteoporosis therapy.9

The WHO defines osteoporosis as severe if patients have a hip BMD level of >2.5 SDs below the mean BMD for young, white, adult women, and have suffered a fragility fracture.5 This definition applies to a substantial portion of women, because 42% of women >50 years of age are predicted to sustain ≥1 fragility fracture in their lifetime.85 Approximately 50% of all fragility fractures in women occur between 67 and 83 years of age, and the risk of fracture increases exponentially with age.85 The lifetime risk of sustaining a hip fracture, clinical vertebral fracture, and other fractures is estimated at 17.0% (95% CI: 16.2; 17.8), 9.6% (95% CI: 9.2; 10.0), and 30.4% (95% CI: 29.1; 31.7) respectively.85 If teriparatide therapy is limited to patients with hip fractures, potentially 3.6% of women with osteoporosis (or 26,000 women in 2006) could receive teriparatide each year. If teriparatide treatment was continued for a full 18-month course of therapy, this number increases to 5.4% or 40,000 women ≥65 years.8 It is estimated that each year, 21,000 (2.2%) of women ≥50 years will suffer a fragility wrist fracture.86 Based on IMS Health Canada data, the Canadian use of teriparatide in its first year of market approval (August 2004 to July 2005) is presented in Appendix 6 Table 15.

6.2 Budget Impact Assessment

6.2.1 Methods

a) Objectives and perspective

The budget impact analysis examines the cost of secondary prevention of osteoporosis in Canada at a macroeconomic level and from a public payer’s perspective.
Table 7: Formulary status of bisphosphonates and teriparatide on Canadian publicly funded drug plans

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Alendronate</th>
<th>Etidronate and Calcium</th>
<th>Risedronate</th>
<th>Teriparatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC</td>
<td>R</td>
<td>F</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>AB(^{87})</td>
<td>R</td>
<td>F</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>SK(^{88})</td>
<td>R</td>
<td>F</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>MB</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>ON</td>
<td>R</td>
<td>F</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>QC(^{89-91})</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>N</td>
</tr>
<tr>
<td>NB(^{92})</td>
<td>R</td>
<td>F</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>NS</td>
<td>R</td>
<td>F</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>PE</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>U</td>
</tr>
<tr>
<td>NL</td>
<td>R</td>
<td>F</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>YT(^{93,94})</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>NIHB(^{95})</td>
<td>F</td>
<td>F</td>
<td></td>
<td>N</td>
</tr>
</tbody>
</table>


The primary purpose is to explore the potential impact of adding teriparatide to publicly funded provincial, territorial, or federal formularies. A secondary analysis examines other potential bisphosphonate budget scenarios, based on the findings of the cost effectiveness analysis.

This budget impact analysis will examine the cost impact of theoretical policy options to provide input to decision makers for consideration in their budget planning. It is not intended to provide an accurate prediction of the actual drug plan expenditures for teriparatide or bisphosphonates.

b) Rationale
The budget impact of listing teriparatide on drug formularies was calculated, based on switch rates rather than the cost of “add on” therapy. The analysis assumes that patients who are prescribed teriparatide represent those with severe osteoporosis who developed a fracture during bisphosphonate therapy. It is assumed that patients switch from a bisphosphonate to teriparatide, and are not treated with both agents concurrently. This was based on a study that evaluated changes in BMD, and found that sequential therapy (PTH followed by alendronate) was superior to concurrent therapy or monotherapy with PTH followed by no drug therapy. If these trends apply to fracture risk, PTH followed by a bisphosphonate would be the preferred sequence of therapy. Sensitivity analysis was conducted for the cost of concurrent therapy.

Switch rates of 2.5%, 3.6%, and 5.0% were based on the incidence of hip and wrist fractures in Canadian women ≥65 years. An estimated 2.2% or 3.6% of women with osteoporosis per year would be treated with teriparatide after a wrist or hip fracture, if teriparatide therapy lasted one year. The portion of women treated annually increases to 3.3% or 5.4% of women with osteoporosis, if
Teriparatide treatment was continued for 18 months. The analysis assumes that women were taking bisphosphonates before fracture, and would restart therapy after teriparatide therapy was complete. A sensitivity analysis was also conducted for switch rates of 1.0%, 7.5%, and 10.0%.

A secondary budget impact analysis was conducted for the bisphosphonates, based on the findings of our cost effectiveness analysis (Table 4). In this analysis, etidronate was dominated in all age groups. As a result, we calculate the incremental cost of funding alendronate in its place. Budget estimates were also calculated, assuming that the funding of bisphosphonates was limited to women ≥80 years. The ICER of alendronate, risedronate, and teriparatide decreases with increasing age. For example, for 80-year-old women, the cost per QALY gained with alendronate is C$13,000. This figure increases to C$169,600 for women 65 years of age, and reflects the low absolute risk of fractures in the younger age groups.

c) Data sources
Provincial bisphosphonate utilization data for 2004 were supplied by seven Canadian publicly funded drug plans. These jurisdictions were included in the analysis.

Population data for 2004 and estimates for 2006 and 2011 were obtained from Statistics Canada. The cost of bisphosphonate products was obtained from provincial online formularies (Appendix 6 Table 1). The cost of teriparatide was supplied by PPS Pharma. All cost data are presented in Canadian dollars, and drug prices are assumed to be fixed.

d) Primary analysis
Drug utilization data from publicly funded drug plans in 2004 were used for the base case analysis. Table 8 summarizes expenditure data in the seven provinces that supplied data. The number of patients who were prescribed bisphosphonates was inferred from the bisphosphonate utilization data (Appendix 6 Table 16). For each product, the total cost per prescription was calculated by dividing the total sales by the number of prescriptions. If disaggregate information on ingredient costs, markup, and professional fees were unknown, an estimated pharmacy fee of C$10 was subtracted from the total cost per prescription to estimate the drug cost per prescription. The days per prescription was estimated by dividing the drug cost per prescription by the median drug cost per day. If the number of tablets per prescription was known, then this was used instead to calculate the number of days per prescription.

The number of years of therapy was calculated by multiplying the total number of prescriptions by the days per prescription, and dividing by 365. We assumed that one year of therapy represents one patient treated for a full year. This method underestimates the number of actual claimants, because not all claimants receive a full year of therapy. This method, however, did provide a consistent means of calculating the number of recipients based on the available information.

The number of patients treated each year was multiplied by the teriparatide switch rates and the annual per patient cost of teriparatide (C$9,713) to calculate the total cost of teriparatide (Table 9).

The cost of bisphosphonates displaced, as patients were switched from bisphosphonates to teriparatide, is shown in Table 10.
Table 8: 2004 Expenditures on bisphosphonates (in C$ millions)

<table>
<thead>
<tr>
<th></th>
<th>PE</th>
<th>NL</th>
<th>NS</th>
<th>ON</th>
<th>MB</th>
<th>SK</th>
<th>BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>etidronate and calcium</td>
<td>$0.024</td>
<td>$0.298</td>
<td>$0.008</td>
<td>$21.666</td>
<td>$0.129</td>
<td>$1.576</td>
<td>$5.902</td>
</tr>
<tr>
<td>alendronate</td>
<td>$0.002</td>
<td>$0.313</td>
<td>$1.844</td>
<td>$28.908</td>
<td>$2.319</td>
<td>$1.921</td>
<td>$2.920</td>
</tr>
<tr>
<td>risedronate</td>
<td>$0.000</td>
<td>$0.127</td>
<td>$1.199</td>
<td>$25.531</td>
<td>$0.386</td>
<td>$0.979</td>
<td>$0.644</td>
</tr>
<tr>
<td>total</td>
<td>$0.027</td>
<td>$0.739</td>
<td>$3.052</td>
<td>$76.105</td>
<td>$2.834</td>
<td>$4.476</td>
<td>$9.465</td>
</tr>
</tbody>
</table>


Table 9: Estimated cost of teriparatide (2004 base year) in C$ millions

<table>
<thead>
<tr>
<th>Switch Rate</th>
<th>PE</th>
<th>NL</th>
<th>NS</th>
<th>ON</th>
<th>MB</th>
<th>SK</th>
<th>BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5%</td>
<td>$0.047</td>
<td>$0.513</td>
<td>$1.379</td>
<td>$58.973</td>
<td>$1.081</td>
<td>$3.213</td>
<td>$8.672</td>
</tr>
<tr>
<td>3.6%</td>
<td>$0.067</td>
<td>$0.739</td>
<td>$1.985</td>
<td>$84.921</td>
<td>$1.556</td>
<td>$4.627</td>
<td>$12.487</td>
</tr>
<tr>
<td>5.0%</td>
<td>$0.093</td>
<td>$1.027</td>
<td>$2.758</td>
<td>$117.945</td>
<td>$2.161</td>
<td>$6.426</td>
<td>$17.344</td>
</tr>
</tbody>
</table>

Table 10: Estimated displaced bisphosphonate expenditures (2004 base year) in C$ millions

<table>
<thead>
<tr>
<th>Switch Rate</th>
<th>PE</th>
<th>NL</th>
<th>NS</th>
<th>ON</th>
<th>MB</th>
<th>SK</th>
<th>BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5%</td>
<td>$0.0007</td>
<td>$0.018</td>
<td>$0.076</td>
<td>$1.903</td>
<td>$0.071</td>
<td>$0.112</td>
<td>$0.237</td>
</tr>
<tr>
<td>3.6%</td>
<td>$0.0010</td>
<td>$0.027</td>
<td>$0.110</td>
<td>$2.740</td>
<td>$0.102</td>
<td>$0.161</td>
<td>$0.341</td>
</tr>
<tr>
<td>5.0%</td>
<td>$0.0013</td>
<td>$0.037</td>
<td>$0.153</td>
<td>$3.805</td>
<td>$0.142</td>
<td>$0.224</td>
<td>$0.473</td>
</tr>
</tbody>
</table>

To determine the incremental costs of teriparatide (i.e., the net budget impact) for each province, the costs of the displaced bisphosphonates were subtracted from the costs of teriparatide.

The base case analysis for 2004 was projected to 2006 and 2011, based on the estimated provincial population growth of women ≥65 years. Women ≥65 years were selected as the most relevant population for growth estimates, based on the prevalence of osteoporosis. Provincial population data, and displaced bisphosphonate and projected teriparatide costs are shown in Appendix 6 Tables 17 to 21.

e) Secondary analysis

A secondary population-based analysis was conducted with the bisphosphonates. Canadian female population data was multiplied by the age-specific prevalence of osteoporosis to determine the number of women with osteoporosis in each age group. The number of women with osteoporosis was multiplied by the annual prescription costs to show the costs if alendronate was funded in place of etidronate, for women ≥65 years and for women ≥80 years.
6.2.2 Results

a) Primary analysis

Tables 11 to 13 show the potential incremental costs to publicly funded drug plans if teriparatide was provided as a limited use benefit. The additional costs of teriparatide are greater than the costs displaced by the bisphosphonates. Incremental costs would be higher if teriparatide and bisphosphonates were prescribed concurrently. The projected incremental costs for Canada were extrapolated, based on the population of women ≥65 years in Canada, relative to the base case provinces.

<table>
<thead>
<tr>
<th>Switch Rate</th>
<th>PE</th>
<th>NL</th>
<th>NS</th>
<th>ON</th>
<th>MB</th>
<th>SK</th>
<th>BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5%</td>
<td>$0.046</td>
<td>$0.495</td>
<td>$1.302</td>
<td>$57.070</td>
<td>$1.010</td>
<td>$3.101</td>
<td>$8.435</td>
</tr>
<tr>
<td>3.6%</td>
<td>$0.066</td>
<td>$0.713</td>
<td>$1.876</td>
<td>$82.181</td>
<td>$1.454</td>
<td>$4.466</td>
<td>$12.147</td>
</tr>
<tr>
<td>5.0%</td>
<td>$0.092</td>
<td>$0.990</td>
<td>$2.605</td>
<td>$114.140</td>
<td>$2.019</td>
<td>$6.202</td>
<td>$16.870</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Switch Rate</th>
<th>PE</th>
<th>NL</th>
<th>NS</th>
<th>ON</th>
<th>MB</th>
<th>SK</th>
<th>BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5%</td>
<td>$0.047</td>
<td>$0.509</td>
<td>$1.335</td>
<td>$59.183</td>
<td>$1.020</td>
<td>$3.130</td>
<td>$8.811</td>
</tr>
<tr>
<td>3.6%</td>
<td>$0.067</td>
<td>$0.734</td>
<td>$1.923</td>
<td>$85.223</td>
<td>$1.468</td>
<td>$4.507</td>
<td>$12.688</td>
</tr>
<tr>
<td>5.0%</td>
<td>$0.094</td>
<td>$1.019</td>
<td>$2.670</td>
<td>$118.365</td>
<td>$2.039</td>
<td>$6.260</td>
<td>$17.623</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Switch Rate</th>
<th>PE</th>
<th>NL</th>
<th>NS</th>
<th>ON</th>
<th>MB</th>
<th>SK</th>
<th>BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5%</td>
<td>$0.051</td>
<td>$0.582</td>
<td>$1.474</td>
<td>$66.023</td>
<td>$1.072</td>
<td>$3.227</td>
<td>$9.992</td>
</tr>
<tr>
<td>3.6%</td>
<td>$0.074</td>
<td>$0.838</td>
<td>$2.123</td>
<td>$95.073</td>
<td>$1.544</td>
<td>$4.647</td>
<td>$14.389</td>
</tr>
<tr>
<td>5.0%</td>
<td>$0.102</td>
<td>$1.164</td>
<td>$2.948</td>
<td>$132.046</td>
<td>$2.145</td>
<td>$6.454</td>
<td>$19.985</td>
</tr>
</tbody>
</table>

In 2004, an additional C$111 million, C$159 million, or C$222 million would be required for all jurisdictions at teriparatide switch rates of 2.5%, 3.6%, or 5.0%. In 2006 and 2011, the additional costs related to the listing of teriparatide would be C$115 million to C$230 million, and C$128 million to C$257 million respectively, depending on the switch rate (Table 14).

b) Secondary analysis

The population-based analysis shows the budget impact of funding bisphosphonates for subgroups with different ICERs (Tables 15 to 17). As the absolute risk of fracture increases with age, the incremental cost per QALY decreases. The prevalence of osteoporosis increases with age and so does the total cost of bisphosphonate therapy.
Table 14: Estimated incremental costs for Canada

<table>
<thead>
<tr>
<th>Year</th>
<th>Switch Rate</th>
<th>Total Impact for Provinces in Base Case Analysis (C$ millions)</th>
<th>Total Estimated Impact for All Jurisdictions (C$ millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>2.5%</td>
<td>$71.459</td>
<td>$110.754</td>
</tr>
<tr>
<td></td>
<td>3.6%</td>
<td>$102.902</td>
<td>$159.486</td>
</tr>
<tr>
<td></td>
<td>5.0%</td>
<td>$142.919</td>
<td>$221.508</td>
</tr>
<tr>
<td>2006</td>
<td>2.5%</td>
<td>$74.035</td>
<td>$114.903</td>
</tr>
<tr>
<td></td>
<td>3.6%</td>
<td>$106.610</td>
<td>$165.460</td>
</tr>
<tr>
<td></td>
<td>5.0%</td>
<td>$148.070</td>
<td>$229.806</td>
</tr>
<tr>
<td>2011</td>
<td>2.5%</td>
<td>$82.422</td>
<td>$128.410</td>
</tr>
<tr>
<td></td>
<td>3.6%</td>
<td>$118.688</td>
<td>$184.911</td>
</tr>
<tr>
<td></td>
<td>5.0%</td>
<td>$164.845</td>
<td>$256.821</td>
</tr>
</tbody>
</table>

Table 15 shows the estimated number of women ≥65 years with osteoporosis in 2006 and 2011 by age; and shows the total annual cost of alendronate therapy. We used the lowest cost alendronate formulation listed on the formularies we surveyed for the analysis (generic alendronate 10 mg).

The cost effectiveness analysis found that etidronate was dominated by alendronate in all age groups. Tables 16 and 17 show the cost impact of funding alendronate in place of etidronate in all women with osteoporosis ≥65 years, or restricted to women ≥80 years. This means that the 20% market share, now held by etidronate, would be taken over by alendronate. The costs incurred by publicly funded drug plans would vary depending on the formulary status (open or limited benefit) of these two agents.

Table 15: Annual cost of alendronate for all women with osteoporosis ≥65 years, by age, 2006 and 2011

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Prevalence of Osteoporosis</th>
<th>Estimated Number of Women with Osteoporosis</th>
<th>Incremental Cost per QALY Alendronate versus No drug therapy</th>
<th>Annual Cost of Alendronate Therapy (in C$ millions)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2006</td>
<td>2011</td>
<td>2006</td>
</tr>
<tr>
<td>65 to 69</td>
<td>18.2 %</td>
<td>115,661</td>
<td>141,250</td>
<td>$169,600</td>
</tr>
<tr>
<td>70 to 79</td>
<td>27.0 %</td>
<td>278,991</td>
<td>291,600</td>
<td>$97,200</td>
</tr>
<tr>
<td>80+</td>
<td>42.1 %</td>
<td>331,959</td>
<td>372,375</td>
<td>$13,000</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>726,611</td>
<td>805,225</td>
<td></td>
</tr>
</tbody>
</table>

* Median annual cost per patient for generic alendronate 10 mg C$444.14 multiplied by number of patients; QALY=quality-adjusted life-years. Source: Tenenhouse et al.,60 Statistics Canada82-84

c) Sensitivity analysis

Appendix 6 Tables 22 to 25 show the budget impact of treating patients with teriparatide and bisphosphonates concurrently (add-on therapy) and the incremental costs of teriparatide for switch rates of 1.0%, 7.5%, and 10.0%. Even with a low rate of teriparatide use, the cost of teriparatide exceeds potential displaced bisphosphonate costs. The budget impact of concurrent therapy is higher than that of sequential therapy.
Table 16: Bisphosphonate budget estimates for women with osteoporosis ≥65 years

<table>
<thead>
<tr>
<th>Year</th>
<th>2004</th>
<th>2006</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>estimated number of women with osteoporosis</td>
<td>685,743</td>
<td>726,611</td>
<td>805,225</td>
</tr>
<tr>
<td>Products Prescribed</td>
<td>Annual Cost per Patient†</td>
<td>Total Drug Budget Cost (C$ millions)</td>
<td>Total Drug Budget Cost (C$ millions)</td>
</tr>
<tr>
<td>base case: alendronate generic (50%), etidronate (20%), risedronate (30%)*</td>
<td>$457</td>
<td>$313.4</td>
<td>$332.1</td>
</tr>
<tr>
<td>alendronate generic (70%), risedronate (30%)</td>
<td>$507</td>
<td>$347.7</td>
<td>$368.4</td>
</tr>
<tr>
<td>incremental costs versus base case</td>
<td>$50</td>
<td>$34.3</td>
<td>$36.3</td>
</tr>
</tbody>
</table>

*Market share based on IMS Health Canada data for 2004. †Annual costs calculated by multiplying annual cost per drug by market share. Alendronate costs based on median cost of 10 mg generic product.

Table 17: Bisphosphonate budget estimates for women with osteoporosis ≥80 years

<table>
<thead>
<tr>
<th>Year</th>
<th>2004</th>
<th>2006</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>estimated number of women with osteoporosis</td>
<td>295,332</td>
<td>331,959</td>
<td>372,375</td>
</tr>
<tr>
<td>Products Prescribed</td>
<td>Annual Cost per Patient†</td>
<td>Total Drug Budget Cost (C$ millions)</td>
<td>Total Drug Budget Cost (C$ millions)</td>
</tr>
<tr>
<td>base case: alendronate generic (50%), etidronate (20%), risedronate (30%)*</td>
<td>$457</td>
<td>$135.0</td>
<td>$151.7</td>
</tr>
<tr>
<td>alendronate generic (70%), risedronate (30%)</td>
<td>$507</td>
<td>$149.7</td>
<td>$168.3</td>
</tr>
<tr>
<td>incremental costs versus base case</td>
<td>$50</td>
<td>$14.7</td>
<td>$16.6</td>
</tr>
</tbody>
</table>

*Market share based on IMS Health Canada data for 2004. †Annual costs calculated by multiplying annual cost per drug by market share. Alendronate costs based on median cost of 10 mg generic product.

7 DISCUSSION

Teriparatide is the first agent that acts by stimulating new bone formation. It is a synthetic, recombinant polypeptide hormone with anabolic effects that can cause an increase in skeletal mass, bone formation and resorption, and bone strength. Bisphosphonates are stable analogues of naturally occurring pyrophosphates. The mechanism of action of these drugs is to inhibit bone resorption through their effects on osteoclasts.

This review provides additional information to be used in decisions regarding access to bisphosphonates and teriparatide. Decision makers must determine whether to make these drugs available, and under what conditions given their acquisition costs, the increasing use of drugs for
the prevention and treatment of osteoporosis, the increased incidence of osteoporosis, the associated morbidity and mortality, and the financial burden of treating the complications of osteoporosis.

7.1 Summary of Results

This evaluation involved a systematic review of the efficacy data for teriparatide in the treatment of osteoporosis in postmenopausal women. The results of a systematic review of the bisphosphonate drugs and the clinical evidence obtained in this report were used to conduct a cost effectiveness analysis. The cost effectiveness analysis was based on an analytic model used in previous studies. We used Canadian data for the cost effectiveness and budget-impact analyses.

7.1.1 Systematic Review of Teriparatide

Two teriparatide studies that met the selection criteria were retrieved. The pooling of results through a meta-analysis was not feasible. One small trial provided comparative effectiveness data between teriparatide and a bisphosphonate (alendronate). Both trials met the criteria for the secondary prevention of fractures.

One study indicated that compared with placebo, teriparatide 20 micrograms administered daily as a subcutaneous injection prevented vertebral and non-vertebral fractures in women with a high risk of fractures. Similar results were obtained with the 40-microgram dose. No significant effect could be identified for hip and wrist fractures. The risk of withdrawals due to adverse events, or any cause, was not statistically different between teriparatide 20 micrograms and placebo. At a dose of 40 micrograms per day, teriparatide caused more withdrawals due to adverse events than placebo. The only active comparison study compared teriparatide 40 micrograms per day to alendronate 10 mg daily. In this study, no differences were found between the two agents in non-vertebral fractures, withdrawals due to adverse events, or any cause.

7.1.2 Systematic Review of Bisphosphonates

The systematic review by Wells et al. showed that the main benefit of the bisphosphonates, relative to placebo, is in the secondary prevention of fractures. The magnitude of this effect varies among bisphosphonates. Etidronate is associated with a reduction in vertebral fractures. Risedronate reduces vertebral, hip, and non-vertebral fractures. Alendronate was associated with a reduction in vertebral, non-vertebral, hip, and wrist fractures; statistical significance was only reached for wrist fractures in the yearly fixed effect analysis.

The available data do not support the use of bisphosphonates in the primary prevention of clinical fractures. Alendronate, however, was shown to be effective in the primary prevention of vertebral fractures.

Indirect comparisons with the bisphosphonates suggest that teriparatide is more effective in the secondary prevention of vertebral fractures; whereas alendronate is more effective in reducing hip and wrist fractures (Appendix 6 Table 11).

7.1.3 Economic Evaluation

The economic analysis was conducted to assess the cost effectiveness of alternative treatment options for women with osteoporosis and previous fractures. Four pharmaceutical treatment
options and a no-drug therapy option were considered. We found that alendronate or no drug therapy was the optimal treatment option. The choice between the two depended on the woman’s age (i.e., alendronate is more cost-effective for women ≥80 years because of the increase in the baseline risk of fractures) and on a decision maker’s maximum willingness to pay for a QALY gained (e.g., ICER of C$169,600 for alendronate versus no drug therapy among women 65 years of age). Risedronate and etidronate were dominated by alendronate or no drug therapy, and were not found to be the most cost-effective under any scenario. Given the data relating to the relative effectiveness of teriparatide and its cost, teriparatide cannot be considered to be cost-effective. Sensitivity analyses showed that the results did not significantly change even when additional analyses were conducted using different discount rates, baseline risk characteristics, and assumptions about drug costs, dosage forms, compliance, and benefit beyond therapy curtailment.

Our base case analysis used the once a day, brand name alendronate product, because this was the product evaluated in the available RCTs. We recognize that generic and once weekly formulations may be more commonly used in Canada, so we tested this possibility in a sensitivity analysis (Appendix 6 Table 13). This analysis confirmed that, in terms of cost effectiveness, alendronate would be even more attractive given the availability of less expensive generic versions of the daily and weekly formulations.

Teriparatide may be considered for patients who are intolerant to bisphosphonates. In this situation, the correct comparison is between teriparatide and no drug therapy. The incremental cost per QALY gained for teriparatide versus no drug therapy is C$851,000 for an 80-year-old woman with a previous fracture. Thus, no drug therapy may be viewed as the cost-effective option if the health care system is unprepared to pay >$50,000 for a QALY.

### 7.2 Study Limitations

The interpretation of the results of this evaluation is limited by several factors.

- The efficacy data for teriparatide were based on two studies only. The ability to generalize the trials’ findings is limited by the population studied (e.g., free of chronically disabling conditions with no exposure to drugs affecting bone or BMD in the previous two to 24 months). The trial with active comparison was small (146 participants). The quality assessment for both trials revealed potential sources of bias, such as unclear allocation concealment.
- In the CADTH review of bisphosphonates, most etidronate trials enrolled a small number of participants (total of 1,248), and were not necessarily designed to measure fractures. The available evidence for alendronate and risedronate is more robust. For risedronate, six RCTs were published, including a total of 13,795 participants. In comparison, 11 RCTs that enrolled a total of 12,099 participants evaluated alendronate.
- The lack of clarity in allocation concealment was common in the bisphosphonate studies. All 11 etidronate trials had an unclear concealment of allocation; three of the 11 alendronate trials had an adequate concealment; and one of the six risedronate trials had an adequate concealment.
- There were large losses to follow-up in the bisphosphonate trials. All six risedronate trials had losses to follow-up of >20%. Three trials for etidronate and alendronate had a >20% loss to follow-up, and in one trial, the percentage lost to follow-up was not reported.
- A potential source of heterogeneity in RCTs is the lack of a uniform definition of non-vertebral fracture. While some researchers may use a liberal definition (any fracture other than a vertebral fracture), others may use a more conservative definition, including only fractures of the hip, clavicle, humerus, wrist, pelvis, or leg.
• One teriparatide trial reported hip and wrist data for the number of women with fractures instead of the total number of fractures. The difference is unlikely to be significant.
• Information on the harm to benefit ratio was unavailable. RCTs tend to be underpowered to detect rare events; so it is difficult to make conclusive statements about adverse events and the long-term tolerability of teriparatide and bisphosphonates. Outside RCTs, concerns exist regarding the safe use of bisphosphonates, particularly alendronate, and to a lesser degree, risedronate, for which esophageal ulcers and gastritis have been reported. The potential risk of osteosarcoma with teriparatide has been raised.33
• Male patients with osteoporosis were not considered in the clinical reviews and economic analysis.
• One study compared teriparatide 40 micrograms daily, a dose higher than the recommended 20 micrograms, to alendronate. No other comparative trials are available, so we based the economic evaluation on indirect comparisons.
• The economic analysis relied on various sources of data. It used Canadian data, however, so it is applicable to the Canadian situation.
• The economic and budget-impact analyses are based on daily dosages for risedronate and alendronate. Both drugs are available in less expensive weekly formulations that may decrease the ICER and alter the incremental budget estimates.
• For the budget impact analysis, we assumed that the bisphosphonate market was saturated; no growth in the treated population was anticipated with the addition of teriparatide to the market.
• Incremental budget estimates for jurisdictions that did not provide bisphosphonate utilization data was inferred, based on population.
• The review of economic analyses included studies published until May 2004. At least two subsequent articles identified by a reviewer have been published since May 2004. Inclusion of these studies in the review would not have changed the conclusion regarding the lack of quality in existing studies.
• For the budget impact analysis, it was assumed that patients who were prescribed teriparatide would otherwise have received a bisphosphonate, and switch rates were modelled based on fracture incidence, because the true rate was unknown.
• For the budget impact analysis, ancillary costs, such as teaching patients how to administer teriparatide injections, were excluded. Plan-specific co-pay portions were not estimated. Generic costs were used for the secondary analysis. These factors may lead to an over- or under-estimate of the actual incremental costs.

7.3 Ability to Generalize Findings

The ability to generalize the clinical findings is limited to women with previous fractures or at a high risk of fractures, who present similar characteristics as the participants in the teriparatide trials (i.e., free of chronically disabling conditions, with no exposure to drugs affecting bone or BMD in the previous two to 24 months). Women with osteoporosis living in the community are more likely to have medical conditions for which they use concurrent therapies. They are also more likely to have tried other drugs to prevent osteoporotic fractures. This should be considered when interpreting the results of our systematic review and economic evaluation. The small number of study participants increases the uncertainty of our findings for teriparatide and etidronate. Additional research is needed to better determine the effects of these drugs. Patients with pre-existing gastrointestinal disorders were excluded in some of the bisphosphonate trials, reducing the ability to generalize study findings to the real world. Our findings provide support for the efficacy of the drugs that we evaluated, but they provide only partial information on their long-term effectiveness.
7.4 Health Services Impact

The budget impact analysis examined the possible costs to publicly funded drug plans if teriparatide was listed as a limited benefit. With an annual cost per patient of C$9,713 compared with the bisphosphonates (C$191 to C$707 per patient), the incremental budget impact is substantial, even if teriparatide is limited to a small portion of patients with osteoporosis. For example, if 2.5% of patients switched to teriparatide, publicly funded drug plans would incur an additional C$111 million in drug costs (2004 estimate). In contrast, a total of C$312 million was spent on bisphosphonates in 2004, including public, private, and out-of-pocket sales.

The secondary analysis shows the budget impact of funding bisphosphonates for different subpopulations based on the ICER. Women >80 years of age treated with alendronate have an incremental cost per QALY gained of C$13,000. This group, however, represents a large portion of women with osteoporosis, and accounts for an estimated C$147 million of C$323 million in total bisphosphonates expenditures (2006 estimate).

In the cost effectiveness analysis, etidronate was dominated by alendronate in all age groups. If all publicly funded drug programs in Canada decided to fund alendronate in place of etidronate, it would result in incremental costs of C$34 million to C$40 million (2004 to 2011) for all women with osteoporosis ≥65 years of age. If funding was limited to women ≥80 years of age, the incremental costs would vary from C$15 million to C$19 million between 2004 and 2011. The costs to publicly funded drug plans would vary depending on the listing status of bisphosphonates.

7.5 Knowledge Gaps

Several research questions still need to be answered.

- What are the relative merits or harm of the bisphosphonates and teriparatide, as measured in head-to-head trials?
- What are the clinical benefits and harm of using teriparatide for women for whom a previous osteoporosis agent has failed?
- What are the clinical benefits and harm of using a teriparatide dose <20 micrograms (e.g., 10 micrograms)?
- What are the clinical benefits, if any, and harm of combining an anti-resorptive agent (bisphosphonates) with a bone anabolic agent such as teriparatide?
- What is the optimal sequence of therapy for all osteoporotic agents?
- Are there populations of women with osteoporosis (e.g., those with other comorbid conditions or concurrent therapies) who are more likely to benefit from or be harmed by teriparatide therapy?
- What is the long-term safety of teriparatide?

8 CONCLUSION

The purpose of this report was to evaluate the clinical and cost effectiveness of teriparatide in relation to the three bisphosphonates available in Canada; alendronate, etidronate, and risedronate. A systematic review of the bisphosphonates and one for teriparatide were used to perform an economic analysis of available and effective osteoporosis drugs. The systematic reviews and economic analysis show the following:
Clinical

- Compared with placebo, teriparatide 20 micrograms administered daily by subcutaneous injection confers a significant reduction in the risk of vertebral and non-vertebral fractures as secondary prevention.
- Teriparatide 40 micrograms daily and alendronate 10 mg daily are not significantly different in the secondary prevention of non-vertebral fractures.
- Teriparatide 20 micrograms per day, the recommended dose, has not been compared in head-to-head fracture trials with any bisphosphonate.
- No trials with teriparatide studied the primary prevention of osteoporotic fractures in women.
- Limited evidence support the use of bisphosphonates in the primary prevention of osteoporotic fractures. Only alendronate has been shown to be effective in primary prevention, and this effect is limited to vertebral fractures.
- Compared with placebo, etidronate is effective in the secondary prevention of vertebral fractures.
- Compared with placebo, alendronate is effective in the secondary prevention of vertebral, non-vertebral, hip, and wrist fractures.
- Compared with placebo, risedronate is effective in the secondary prevention of vertebral, non-vertebral, and hip fractures.

Economic

- Alendronate or no drug therapy is the optimal treatment option. The choice between the two depends on the woman’s age (i.e., alendronate is more cost-effective for women ≥80 years because of an increase in the baseline risk of fracture), and the maximum willingness of decision makers to pay for a QALY gained (e.g., ICER of C$169,600 for alendronate versus no drug therapy among women 65 years of age).
- Teriparatide is not cost-effective compared to bisphosphonates under any scenario.
- If no drug therapy is the only available alternative, then teriparatide in an 80-year-old woman with a previous fracture is cost-effective if the health care system is prepared to pay C$851,000 for a QALY.
- Etidronate was dominated by alendronate in all age groups.
- It is estimated that by 2006, if teriparatide were listed as a limited use benefit on publicly funded drug plans, governments could incur C$115 million to C$230 million in additional drug costs, depending on the utilization, and the number of patients treated.
9 REFERENCES


APPENDICES

Available from CADTH’s web site
www.cadth.ca