Odanacatib belongs to a new class of osteoporosis drugs designed to block cathepsin K, a lysosomal protease that plays a role in the function of osteoclasts. By inhibiting cathepsin K, odanacatib reduces bone resorption by osteoclasts. Odanacatib is not currently licensed for sale in Canada or the United States.

Current evidence on the safety and efficacy of odanacatib for postmenopausal osteoporosis is limited by the small number of participants who enrolled in one phase 2 trial and its extension studies, and the use of surrogate measures of efficacy.

The phase 2 trial assessed the efficacy of odanacatib compared with placebo for the treatment of postmenopausal women with low bone mineral density who had not previously experienced a fragility fracture. Patients excluded from the trial were women who had ever used intravenous bisphosphonates; received treatment with oral bisphosphonates, estrogen replacement therapy, or raloxifene within the previous six months; or received treatment with teriparatide within the previous 12 months.

Results of the phase 2 trial and its extension studies showed progressive increases in bone mineral density at the lumbar spine, total hip, femoral neck, and trochanter in postmenopausal women who were continuously treated with odanacatib for up to five years. A rapid reversal of the antiresorptive effect was observed in women who discontinued treatment with odanacatib, resulting in a reduction in bone mineral density at all sites toward baseline levels.

The overall incidence of adverse events of odanacatib during the phase 2 trial and its extension studies was generally similar to placebo, and no dose-related trends were observed.

It is not yet known whether odanacatib reduces the risk of fracture or has clinical advantages over currently available therapeutic options. A phase 3 trial is currently assessing the long-term safety and efficacy of odanacatib compared with placebo for the prevention of hip, vertebral, and non-vertebral fractures in women with postmenopausal osteoporosis who have not previously experienced a hip fracture or received pharmacologic treatment for osteoporosis prior to trial initiation. This study did not use an active treatment as a comparator or include Canadian study sites. Pending the results, industry may file a submission in 2013 with regulatory authorities for the approval of odanacatib for the treatment of postmenopausal osteoporosis.

Bone loss occurs when the rate of bone resorption by osteoclasts exceeds the rate of bone formation by osteoblasts during the bone remodelling process. Progressive bone loss leads to the deterioration of bone tissue, low bone mineral density, skeletal fragility, and eventually osteoporosis. Individuals with osteoporosis are at an increased risk for fractures — particularly at the hip, spine (vertebral fractures), and wrist (non-vertebral fractures).

Currently available treatments are limited by moderate-to-poor clinical efficacy for the prevention of fractures (particularly hip and other non-vertebral fractures), adverse effects, patient comorbidities, and poor compliance. Oral bisphosphonates are the most commonly prescribed treatment for osteoporosis, but compliance is limited by gastrointestinal intolerance, and discontinuation rates
of greater than 50% have been reported within 12 months of starting treatment. Furthermore, concerns have been raised regarding the safety of long-term bisphosphonates use. Osteonecrosis of the jaw has been observed in patients receiving long-term, high-dose intravenous bisphosphonates for cancer. Whether the lower-dose bisphosphonate therapy used for osteoporosis increases the risk for osteonecrosis of the jaw over that observed in untreated patients of similar age and frailty has yet to be confirmed. Other adverse effects, including atypical fractures of the femur and esophageal cancer, have been reported in patients receiving long-term bisphosphonate therapy, but there is currently not enough evidence to establish a causative link.

The Technology

Odanacatib (Merck & Co., Inc.) belongs to a new class of osteoporosis drugs designed to selectively block cathepsin K, an osteoclast lysosomal protease responsible for the breakdown of bone collagen. By inhibiting cathepsin K, odanacatib reduces bone resorption by osteoclasts. Although cathepsin K is primarily expressed in osteoclasts, it has also been found in other cell types, including synovial fibroblasts, skin fibroblasts, macrophages, dendritic cells, chondrocytes, epithelial cells of various tissues, melanocytes, and tumour cells. Potential adverse effects of cathepsin K inhibition may be the result of “off-target” inhibition of other cathepsins or by inhibition of cathepsin K in cells other than osteoclasts.

The development of two previous investigational cathepsin K inhibitors, balicitab and relacatib, has been halted. Investigation of balicitab was discontinued when serious dermatological adverse effects (including scleroderma and morphea-like skin lesions) and an increased risk of upper respiratory tract infections were observed during a phase 2 clinical trial. Clinical development of relacatib ceased after the completion of an unpublished phase 1 trial.

Regulatory Status

Odanacatib is not currently licensed for sale in Canada or the United States. Pending results from a phase 3 trial, industry may file a submission in 2013 with regulatory authorities for the approval of odanacatib for the treatment of postmenopausal osteoporosis.

Patient Population

Postmenopausal osteoporosis occurs when a fall in estrogen levels causes the rate of bone resorption to increase, resulting in excessive bone loss. Osteoporosis affects more than 1.5 million Canadians. The prevalence of osteoporosis has been estimated to increase from 6% of women aged 50 to 59 years, to more than 40% of women aged 80 years and older. Frailty fractures represent 80% of all fractures in menopausal women older than 50 years. Fractures increase the risk of chronic pain, bone deformity, depression, long-term disability, and mortality. Fragility fractures have been associated with extended hospital stays, increased wait times for orthopedic surgery and long-term care beds, and substantial health care costs. It is estimated that the annual cost of acute care hospitalizations for fragility fractures in Canada is C$1.2 billion, with the annual cost of hip fractures alone being C$618.6 million. Given the increasing proportion of adults older than 50 years, the annual cost of hip fractures alone is projected to increase to C$2.4 billion by 2041.

Current Practice

Given that various clinical factors can increase the risk of fracture independent of a low bone mineral density, Osteoporosis Canada guidelines recommend that the initiation of pharmacologic treatment for osteoporosis should be based on an assessment of the absolute fracture risk using a validated fracture prediction tool such as the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) tool or the World Health Organization (WHO) Fracture Risk Assessment (FRAX) tool. Both have been calibrated to estimate the 10-year risk of a major fragility fracture in Canadians. Osteoporosis is defined by the presence of a fragility fracture, a bone mineral density of more than 2.5 standard deviations below peak bone mass in an individual older than 50 years (T-score of less than 2.5) in the absence of a fragility fracture, or a high (> 20%) 10-year risk of fracture using the CAROC or FRAX tools.
Pharmacological therapy is now considered in all patients at high (> 20%) 10-year risk of fracture and selected patients at moderate (10% to 20%) 10-year risk of fracture, but not in patients who are estimated to be at low (< 10%) 10-year risk of fracture. Oral bisphosphonates (alendronate and risedronate) are the most commonly used first-line treatment for the prevention of fractures in postmenopausal women, in conjunction with calcium and vitamin D supplementation, and lifestyle measures (such as appropriate diet, regular exercise, and smoking cessation). Other first-line treatment options include an intravenous bisphosphonate (zoledronic acid), a monoclonal antibody (denosumab), a bone-forming agent (teriparatide), a selective estrogen receptor modulator (raloxifene), and estrogen replacement therapy. Calcitonin or etidronate are considered second-line alternatives for the prevention of fractures in postmenopausal women who do not tolerate first-line therapies.

**Methods**

**Literature Search Strategy**

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, Embase, PubMed, The Cochrane Library (2011, Issue 11), and the University of York Centre for Reviews and Dissemination (CRD) databases. Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist. No methodological filters were applied. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and November 7, 2011. Regular alerts were established on Embase, MEDLINE, and PubMed; and information retrieved through alerts was current to December 21, 2011.

**Study Selection Criteria**

Studies evaluating the clinical efficacy and safety of odanacatib compared with placebo or pharmacologic therapies for the treatment of postmenopausal osteoporosis were considered for inclusion in this bulletin. Data from unpublished and published studies were included. Editorials, letters, and literature reviews were excluded.

**The Evidence**

One phase 2 trial and its extension studies assessing odanacatib for the treatment of postmenopausal osteoporosis was identified. The results are summarized in Table 1. Two phase 2 trials and one phase 3 trial evaluating the effect of odanacatib on bone mineral density in postmenopausal women have been completed, but results have not yet been published. A phase 3 trial investigating the effect of odanacatib on bone mineral density in osteoporotic postmenopausal women previously treated with alendronate has been planned, but is not yet open for participant recruitment. An ongoing phase 3 trial is evaluating the safety and efficacy of odanacatib for the prevention of fractures in postmenopausal women with osteoporosis.

A multi-centre, randomized, double-blinded, placebo-controlled phase 2 trial was conducted to assess the efficacy of odanacatib for the treatment of postmenopausal women with low bone mineral density. The base study was conducted as a one-year dose-finding study with a planned one-year extension phase. A total of 399 healthy postmenopausal women (mean age 64.2 ± 7.8 years) with low bone mineral density (T-score between −2.0 and −3.5 at the lumbar spine, femoral neck, trochanter, or total hip) were enrolled. Women with a history of fragility fracture after menopause, or metabolic bone disorders other than osteoporosis, were excluded from the trial. Also excluded from the trial were those who had ever used intravenous bisphosphonates; had received treatment with oral bisphosphonates, estrogen replacement therapy, or raloxifene within the previous six months; or had received treatment with teriparatide within the previous 12 months.

Participants were allocated to one of the weekly odanacatib treatment groups (3 mg, 10 mg, 25 mg, or 50 mg orally) or placebo. Treatment was double-blinded for the first 12 months, but sponsor blinding was not maintained after 12-month analyses were completed. In addition to treatment with odanacatib, all participants received open-label supplemental vitamin D₃ (5,600 IU once weekly) and calcium (500 mg daily if average daily calcium intake was less than 1,000 mg). The primary end point was the percentage change from baseline in lumbar spine bone mineral density. Secondary end points included percentage change from baseline in bone mineral...
density at the femoral neck, trochanter, and total hip; percentage change from baseline in the levels of bone resorption markers and bone formation markers; and safety assessments.

Measurement of the primary end point from baseline to two years showed that odanacatib reduced bone resorption and progressively increased lumbar spine bone mineral density in a dose-dependent manner.\textsuperscript{33} Similar results were reported for secondary end point measurements at other sites, with dose-dependent increases in bone mineral density at the total hip, femoral neck, and trochanter over two years. In contrast, bone mineral density at all sites was either unchanged or decreased from baseline in the placebo group. Consistent with an antiresorptive effect, markers of bone resorption decreased throughout the two years of treatment in the three highest dosage groups. Markers of bone formation also decreased in response to treatment with odanacatib. In general, the decreases in bone formation markers in the 50 mg group were lower in magnitude than the changes in levels of bone resorption markers.

Extension studies\textsuperscript{34,35} were initiated at years three and four to evaluate the long-term safety and efficacy of treatment with odanacatib and the effect of treatment discontinuation. In year three, 189 participants were re-randomized to odanacatib 50 mg weekly (N = 97) or placebo (N = 92) for an additional 12 months.\textsuperscript{34} In years four to five, women who had received placebo or 3 mg odanacatib in years one to two and placebo in year three were switched to 50 mg odanacatib.\textsuperscript{35,36} All others continued with their year three regimen. A total of 100 women received 50 mg odanacatib and 41 received placebo.

Results from the extension studies showed that the women who continued to receive odanacatib at year three and year five showed progressive improvement in bone mineral density at the lumbar spine, total hip, femoral neck, and trochanter.\textsuperscript{34-36} Discontinuation of treatment with odanacatib at two years resulted in a reversal of the antiresorptive effect, with a rapid decrease toward baseline levels in bone mineral density at all sites at year three and year five. Bone resorption markers remained below baseline levels in women who continued to receive odanacatib at year three and year five. Upon discontinuation of odanacatib in year two, increases in bone turnover markers suggested that the antiresorptive effect of odanacatib is reversible within a short time frame.\textsuperscript{34} The increase in bone turnover markers with treatment discontinuation was not always sustained in year five, the clinical significance of which is not clear.\textsuperscript{36}

Serum tartrate-resistant acid phosphatase 5b (TRAP5b) is a serum marker thought to reflect the presence of viable osteoclasts.\textsuperscript{42} It has been speculated that preserving osteoclast viability allows for the production of signaling factors that stimulate the bone formation process despite the suppression of bone resorption.\textsuperscript{42} Although levels of TRAP5b increased above baseline in all the groups, these levels were consistently higher in patients who continuously received treatment with odanacatib compared with those who discontinued treatment. More studies are needed to determine whether treatment with odanacatib results in a net bone formation effect as a result of a decoupling between resorption and formation during the bone remodelling process.
Total daily intake from both dietary and supplemental sources of approximately 1,200 mg). Approximately 16,200 women aged 65 years or older with low bone mineral density have been randomized at 380 centres worldwide. The primary efficacy outcomes are the number of participants who experience morphometric vertebral fracture, time to first hip fracture, and time to first non-vertebral fracture. Secondary end points include the number of clinical vertebral fractures, changes in bone mineral density, height loss, changes in bone turnover markers, safety, and tolerability. Participants will be followed for up to five years. The expected completion date is November 2014.
Adverse Effects

In general, the overall incidence of adverse events of odanacatib during the phase 2 base study and its extension to five years was similar to placebo, and no dose-related trends were observed. The serious drug-related morphea-like skin lesions and upper respiratory tract infections that were previously observed with balicatib did not occur with odanacatib treatment. During the third year of study, more urinary tract infections or cystitis were observed in the odanacatib group (N = 12; 12.4%) than the placebo group (N = 3; 3.3%). None of these events were classified as drug-related by study investigators or led to discontinuation of the study drug, and all resolved following antibiotic therapy.

Cost

The manufacturer’s price for odanacatib is currently unavailable, as odanacatib has not yet been approved for sale in Canada.

Concurrent Developments

Odanacatib has been investigated for other indications in addition to use in women with postmenopausal osteoporosis. A two-year phase 3 trial is evaluating the safety and efficacy of odanacatib compared with placebo for osteoporosis in men. Results from a four-week phase 2 trial suggested that odanacatib may have similar effectiveness to zoledronic acid for the treatment of metastatic bone disease in women with breast cancer. It is unclear whether odanacatib will be further investigated for reducing the risk of metastatic bone disease, as phase 3 trials designed to study women with breast cancer and men with prostate cancer were halted prior to enrollment. Several other drugs to treat postmenopausal osteoporosis are under development. A phase 3 trial is currently evaluating the safety and efficacy of BA058 (a parathyroid hormone-related peptide) compared with teriparatide or placebo for the prevention of vertebral fractures in postmenopausal women. Other investigational agents currently in phase 2 development for postmenopausal osteoporosis include another cathepsin K inhibitor (ONO-5334 and two monoclonal antibodies (AMG 785 and LY2541546) to sclerostin (a protein that stimulates bone formation).

Rate of Technology Diffusion

Current evidence on the safety and efficacy of odanacatib for postmenopausal osteoporosis is limited by the small number of participants enrolled in each arm of the phase 2 trial, potential biases in the characteristics of participants who elected to continue in the extension studies, and the use of surrogate measures of efficacy. Furthermore, resorption marker data from the phase 2 trial are difficult to interpret because the collagen degradation products that result from cathepsin K are known to differ from those produced by the activity of other osteoclast enzymes. Whether the short-term effects of odanacatib on bone mineral density and bone turnover markers translate into clinically meaningful effects on the risk of fracture in different patient populations will need to be determined with larger long-term clinical trials such as the ongoing phase 3 clinical trial.

Implementation Issues

There is evidence that the use of odanacatib in postmenopausal women with osteoporosis is associated with progressive increases in bone mineral density at the spine and hip, and reductions in bone resorption markers. The clinical significance of the effect of odanacatib on these surrogate measures of efficacy is not yet known. A phase 3 trial is currently assessing the long-term safety and efficacy of odanacatib for the prevention of fractures in postmenopausal women. This study did not use an active treatment as a comparison or include Canadian study sites. Potential cost-consequences of introducing odanacatib to the market will not be known until comparative trials with other osteoporosis therapies are conducted. In addition to establishing the efficacy of odanacatib for preventing fractures in postmenopausal women, a critical issue for introduction into clinical practice will be long-term tolerability and safety relative to other treatment options.


---

Odanacatib for Postmenopausal Osteoporosis
Odanacatib for Postmenopausal Osteoporosis

Cite as: Ndegwa, S. Odanacatib for Postmenopausal Osteoporosis [Issues in Emerging Health Technologies Issue 119]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2012. 

Issues in Emerging Health Technologies is a series of concise bulletins describing drug and non-drug technologies that are not yet used (or widely diffused) in Canada. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada.

While CADTH has taken care in the preparation of this publication to ensure that its contents are accurate, complete, and up to date as of February 2012, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this publication or in any of the source documentation.

This document and the information provided in this document are prepared and intended for use in the context of the Canadian health care system. Other health care systems are different; the issues, information related to the subject matter of this document may be different in other jurisdictions and, if used outside of Canada, it is at the user’s risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH is funded by 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. CADTH 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.

Copyright © CADTH 2012. You are permitted to reproduce this document for non-commercial purposes, provided it is not modified when reproduced and appropriate credit is given to CADTH. You may not otherwise copy, modify, translate, post on a website, store electronically, republish, or redistribute any content from this document in any form or by any means without the prior written permission of CADTH.

Please contact CADTH’s Vice-President of Corporate Services at requests@cadth.ca with any inquiries about this notice or other legal matters relating to CADTH’s services.

ISSN: 1488-6324 (online)