

***Australia's Centralized
Cost-Effectiveness
Requirement for
Pharmaceuticals:
Potential Implications
for U.S. Patients***

Report prepared by
IMS Consulting

January 2006

© 2006. IMSWorld Publications Ltd. All rights reserved.

The material contained in this Report is confidential and proprietary to IMSWorld Publications Ltd., a business unit of IMS. The material is submitted only for the purpose of the Client evaluation of the Report. No rights in said material are hereby transferred to the Client. The material may not be disclosed, duplicated, or otherwise revealed in whole or in part without the written permission of IMSWorld Publications Ltd.

Information you provide may be collected and automatically stored on our database and may be used to send you additional information about IMS group services. Such information also may be transferred to IMS companies based in Switzerland and the United States. If you do not wish to receive further information from IMS, please contact IMS AG Customer Services, 7 Harewood Ave., London NW1 6JB.

TABLE OF CONTENTS

- 1. Summary of Findings 2**
- 2. Project Background 2**
- 3. Methodology 5**
 - Estimating Patient Numbers 5
 - Drug Patient Estimate Methodology* 5
 - Forecasts 6
 - Estimating Usage for Indications Identified by U.S. Guidelines 7
- 4. Key Findings 7**
 - Osteoporosis and Paget’s Disease 7
 - Disease Overview* 7
 - Medicines and Guidelines* 7
 - Patient Impact* 8
 - Alzheimer’s Disease 10
 - Disease Overview* 10
 - Medicines and Guidelines* 11
 - Patient Impact* 11
 - Orphan Drugs 13
 - Disease Overview* 13
 - Medicines and Guidelines* 14
 - Patient Impact* 14
- 5. Conclusion 15**
- 6. References 16**

I. SUMMARY OF FINDINGS

Based on utilization estimates for 2004, this report finds that, if the U.S. government applied cost-effectiveness standards similar to those in Australia, millions of patients nationwide would face significant new barriers to obtaining medicines that they currently receive to treat serious and life-threatening diseases.¹ These barriers potentially could affect millions of patients who are over age 65 and eligible for Medicare.

Patients who would be affected include:

- More than 400,000 Alzheimer’s disease patients, most of whom are eligible for Medicare (over age 65).
- More than 9.1 million patients—a number including more than 3 million Medicare-age patients—with osteoporosis who are taking Fosamax® (alendronate) and Forteo® (teriparatide).
- Thousands of patients with the rare disorders of pulmonary arterial hypertension and essential thrombocythemia.

Many of the drugs in this study are new to the U.S. market, and prescribing of these drugs is growing rapidly. Therefore, an estimated number of patients currently using the drugs accounts for only a small proportion of the total number of patients who may be impacted if the U.S. health care system applied restrictions similar to those employed by Pharmaceutical Benefits Advisory Committee (PBAC).

2. PROJECT BACKGROUND

The use of comparative and cost-effectiveness data on prescription drugs and other health interventions remains a subject of many debates by U.S. policymakers and the media. Indeed, some have called for federal health agencies, such as the U.S. Food and Drug Administration or Centers for Medicare and Medicaid Services to consider cost-effectiveness when making regulatory or coverage decisions for new products.

Australia’s PBAC was among the first regulatory bodies to demand pharmacoeconomic evidence to support applications for reimbursement. As such, it offers potentially useful insight into the possible impact of a centralized, mandatory cost-effectiveness standard in the United States.

Pharmacoeconomic data, which include cost-effectiveness data, are extensively used in the United States but not in the centralized, mandatory way they are employed by Australia. In the United States, this type of data is most commonly demanded in a pluralistic, private-sector delivery system that includes multiple, competing health insurers. The types of economic data used and the ways in which the data are used vary considerably across plans. However, economic data are considered only secondary to clinical safety and effectiveness data and typically are used to set payment policy, not to determine whether the product will be covered at all.

The PBAC, on the other hand, makes recommendations on whether to list the product on Australia’s Pharmaceutical Benefits Scheme (PBS), also known as the “positive list.” This list comprises the drugs that will be made available to Australian patients, and, thus, exclusion from the list represents a broad non-coverage decision. In making recommendations, the PBAC may take into account advice

from a number of sources. These include its Economics Sub-Committee, which was established in 1993 and which reviews and interprets economic analyses of drugs submitted to PBAC, and its Drug Utilization Sub-Committee, which was established in 1988 to collect and analyze data on drug utilization in Australia.

Only drugs deemed safe, effective, cost-effective at the selling price, and in line with “community need” are included on the PBS, the reimbursement “positive list” in Australia. When considering a submission for listing a medicine on the PBS, the PBAC takes into account a number of factors, including:

- The conditions for which the drug has been approved for use in Australia by the Therapeutic Goods Administration. The PBAC only recommends the listing on the positive list of a medicine for use in a condition that is in accordance with the Australian Register of Therapeutic Goods.
- The conditions in which use has been demonstrated to be effective and safe compared to other therapies.
- The costs. The PBAC is required to ensure that money the community spends in subsidizing the PBS represents cost-effective expenditure of taxpayers’ funds. The PBAC may consider a range of other factors and health benefits, including, for example, costs of hospitalization or other alternative medical treatments that may be required, as well as less tangible factors, such as patients’ quality of life. In practice, however, because hospitalization and other costs are borne by other government agencies, these broader costs often are not considered.
- Community need for the pharmaceutical under consideration.

Following recommendation by the PBAC, these processes need to be completed before the medicine can be listed on the PBS:

- Consideration by the Pharmaceutical Benefits Pricing Authority (PBPA).
- Pricing negotiations between the manufacturer and the Department of Health and Aging.
- Finalization of the details for listing the medicine on the PBS.
- Quality and availability checks.
- Consideration by government.

Once the PBAC makes a recommendation to list a medicine on the PBS, the decision moves to the relevant government agencies. It is often not possible to say how long these processes may take to be completed because negotiations regarding the listing details and PBS costs can be complex. In addition, many aspects of the decision-making process are not made publicly available. Currently, the usual minimum time for these processes to be completed is about five months. The Australian system has been found to be significantly slower to provide broad dissemination of new drugs than that of the United States.

The purpose of this report is to examine the standards Australia uses to grant reimbursement “listing” (coverage) to new medicines, in particular, its cost-effectiveness standard. Recent PBAC decisions on specific medicines will be used to quantify and illustrate the extent to which application of a similar standard in the United States could impact patients.

Use of a cost-effectiveness standard is one part of the PBAC effort to restrain spending on pharmaceuticals. However, while PBAC has been criticized for some of its more restrictive decisions, the hoped-for reduction in pharmaceutical spending has not materialized.

This raises the question of whether cost-effectiveness analysis is in fact an effective cost-containment tool. Some U.S. health experts have pointed out that by quantifying the value of pharmaceuticals compared to other health interventions, cost-effectiveness analysis can lead to increased spending on pharmaceuticals.²

While spending on medicines in Australia is rising, the purpose of this paper is not to enter the debate about how much Australia should be spending on medicines. Rather, it seeks to draw lessons about the operation of centralized government decision-making on cost-effectiveness from Australia that may be informative for U.S. policymakers.

The Pharmaceutical Research and Manufacturers of America (PhRMA) approached IMS Management Consulting to assist in developing a perspective on Australia's use of cost-effectiveness as a factor in deciding whether to provide reimbursement for a number of new medicines under its PBS.

IMS and PhRMA have identified seven products recently excluded from reimbursement or reimbursed with stringent guidelines in Australia. These products from the first half of 2004 were identified because they were publicly available on the PBAC website. Less recent decisions are not made readily available and so were not included. The PBAC recently has made a number of additional recommendations to exclude medicines from reimbursement in Australia. Additional research may be warranted on the impact that similar exclusions would have in the United States. Since adopting a cost-effectiveness standard, Australia has denied listing to many other medicines because they did not meet the government's cost-effectiveness standard. The following products were selected for this analysis.

Osteoporosis therapies:

- Actonel® (risedronate)
- Forteo (teriparatide)
- Fosamax (alendronate)

Alzheimer's therapies:

- Namenda® (memantine)
- Reminyl® (galantamine) (now Razadyne™*)

Pharmaceuticals for rare disorders:

- Agrylin® (anagrelide)
- Tracleer® (bosentan)

Based on the nature of the exclusion by PBAC, projected utilization of this group of products in the U.S. market has been assessed.

The objective of this exercise has been to estimate the probable impact, in terms of number of patients affected, if a similar ruling were applied across the U.S. health care system.

At the root of this discussion is the appropriateness of the criteria utilized by the Australian authorities in the formulation of their positive list. Pharmacoeconomic measures have long been the subject of heated debate in a wide number of countries around the world. This study will highlight some potential flaws inherent in a treatment algorithm, based purely on a perceived cost/benefit relationship when viewed in the light of U.S. standards of care and methods of health care delivery and decision-making.

*Reminyl (galantamine) was renamed and will be referred to as Razadyne throughout this paper.

3. METHODOLOGY

Many of the drugs in this study are new to the U.S. market, and prescribing of these drugs is growing rapidly. For this reason, the methodology for this project has had three phases:

1. Identifying the total number of patients who used each product in the year to September 2003 in the U.S. market (where information was available).
2. Obtaining forecasts of the volume sales to September 2008 from IMS standard-unit sales data.
3. Calculating the potential maximum number of patients who may be impacted if the United States implemented the same regulatory framework as Australia (2003–2008).

Estimating Patient Numbers

IMS data do not record incidence or prevalence of diseases. For this study, data were collected from a number of sources to compare several estimates of absolute patient numbers for each product and to validate estimates.

Drug Patient Estimate Methodology

This methodology combines data from National Prescription Audit Plus™ (NPA Plus) and National Disease and Therapeutic Index™ (NDTI) unique patient data.

- **NPA Plus** measures the outflow of dispensed prescriptions from retail, mail order, and long-term care pharmacies into the hands of consumers.
- **NDTI** provides statistical information about the disease and treatment patterns encountered in office-based practices in the United States. The following specialities relevant to this project are covered in the NDTI: orthopedic surgery, psychiatry, pulmonary diseases, and osteopathy.

The equation used to calculate the patient numbers is:

$$\text{Patients Taking Product} = \frac{\text{Dispensed New Rx for Product}}{\text{Average New Rxs/Patient/Year for Product}}$$

Sources: NPA Plus (numerator) and NDTI (denominator).

The number of patients taking a drug is estimated as the number of new prescriptions dispensed for the drug over a 12-month period divided by the average number of new prescriptions each patient receives per year.

This methodology gives the most accurate estimates for products that are sold predominantly through the retail, mail order, and long-term care channels.*

In this study, the products that have the most accurate patient populations from the drug patient estimate methodology are Actonel (risedronate), Agrylin (anagrelide), Forteo (teriparatide), Fosamax (alendronate), and Razadyne (galantamine).

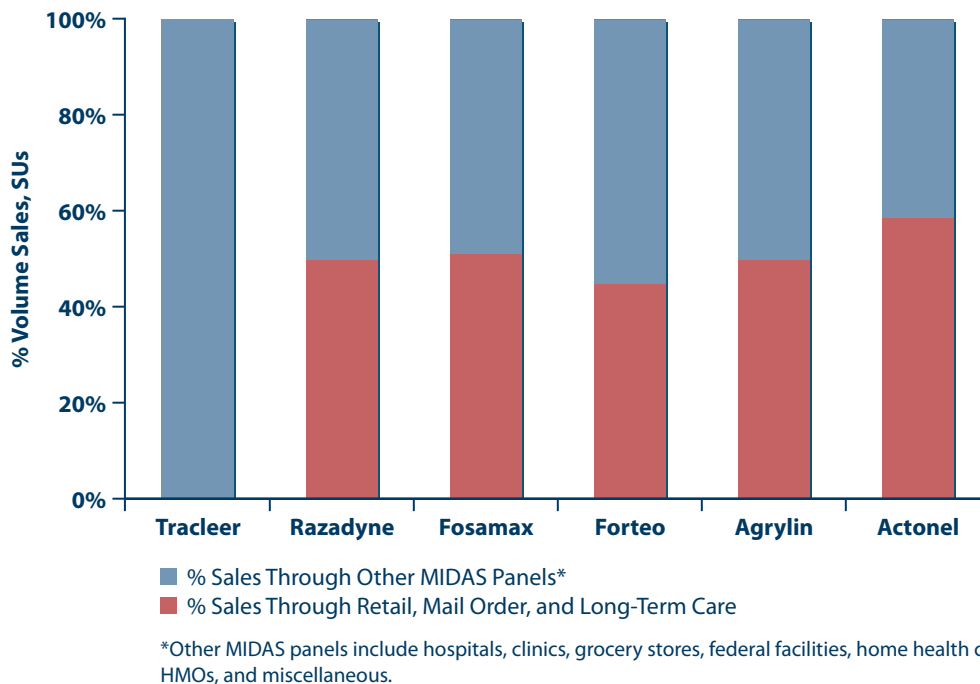
Patient numbers were factored to account for sales panels that are not included in the drug patient estimate methodology.

Numbers obtained using this methodology were verified against U.S. longitudinal prescription data. Longitudinal prescription data offer insights into U.S. physician prescribing dynamics and patient group profiles over time. These data are collected from unique patient identifying numbers that indicate the numbers of patients who have used these products in the last year in the retail sector.

*Namenda (memantine) was approved for use in Alzheimer's patients. The percent sales through the United States MIDAS™ data panels capturing sales of each product year to September 2003 was not available for Namenda (memantine) because it was not approved for use until October 16, 2003.

Figure 1

% Sales Through U.S. MIDAS Data Panels Capturing Sales of Each Product Year to September 2003



Forecasts

To create forecasts of patients for each therapy, one of three methods was applied.

- i. If historical data were available for the product, the standard units were projected to create a baseline. The baseline was then adjusted to take into account any future events on the market to create a forecast. Annual standard units were then divided by an average daily dose (AVDD) to obtain the number of days of therapy. The number of days of therapy was then divided by compliance to obtain the number of patients treated. The AVDD data were obtained from MIDAS, and the compliance rate was estimated from literature and from research with opinion leaders conducted for IMS Therapy Forecaster. The 2003 patient number was then validated against the patient estimates obtained. The

patient forecasts were then validated against Therapy Forecaster or analyst sales forecasts.

2. To forecast the number of patients for Namenda (memantine), an analogue was applied to the data. Namenda (memantine) was first launched in Germany and had a significant impact on the market. This impact was then applied to the U.S. market, and the number of standard units for Namenda (memantine) was generated. The above method was then applied to calculate the number of patients.
3. To forecast the number of patients for Forteo (teriparatide), analyst forecasts were used as an indicator of growth and to validate the forecast number of patients. Standard units were used to obtain the number of patients for the first year, and cost assumptions were made to obtain sales, which were then validated against analyst figures.

Estimating Usage for Indications Identified by U.S. Guidelines

IMS Prescribing Insights data are available only for the retail sector. We examined the diagnoses for which these products have been prescribed in the retail setting using the guidelines given in Figure 1. The following diagnoses were used to estimate the level of prescribing for the correct indication (*International Statistical Classification of Diseases and Related Health Problems* (procedural coding system), 10th edition).

Osteoporosis and Paget's Disease

Fosamax (alendronate) and Actonel (risedronate):

M819 Osteoporosis Unspecified

M859 Diseases of Bone Density and Structure Unspecified

M810 Postmenopausal Osteoporosis

M898 Other Specific Diseases of the Bone

M809 Osteoporosis and Pathological Fracture

Paget's disease applies only to Fosamax (alendronate) and Actonel (risedronate).

Forteo (teriparatide):

M810 Postmenopausal Osteoporosis

M809 Unspecified Osteoporosis with Pathological Fracture

Alzheimer's Disease

G30 Alzheimer's Disease

F03 Unspecified Dementia

Orphan Drugs

Tracleer (bosentan):

I27 Other Pulmonary Heart Disease

Agrylin (anagrelide):

D752 Essential Thrombocytosis

D473 Essential Thrombocythemia

C92 Myeloid Leukemia

D45 Polycythemia Vera

D46 Myelodysplastic Syndromes

D471 Chronic Myeloproliferative Disease

D469 Myelodysplastic Syndrome Unspecified

According to IMS retail data, these products are not co-prescribed.

4. KEY FINDINGS

Osteoporosis and Paget's Disease

Disease Overview

Osteoporosis is a serious health condition that affects more than 44 million Americans. The human and economic costs for this condition may account for approximately \$17 billion (2004) in direct expenditures in hospitals and nursing homes, and that annual expense is expected to triple by 2040.

For the United States in 1995, osteoporotic fractures accounted for 432,000 hospital admissions, almost 2.5 million physician visits, and 180,000 nursing home admissions. About 10 million Americans have osteoporosis, and 34 million more are at risk of developing the disease. Of these 10 million, nearly 80 percent are women. It is estimated that 13–18 percent of postmenopausal white women in the United States have the disease, with an additional 30–50 percent (13–17 million) having low bone mineral density (osteopenia), placing them at increased risk of developing osteoporosis and fractures. Osteoporosis is less common among men, African Americans, and Hispanic women, but this disease is still by no means rare in these populations.

Recognition and treatment of osteoporosis has increased noticeably in the past 10 years. This is thought to be due to the emergence of new treatments, increased marketing of these osteoporosis treatments, and increased public awareness and improvements in screening technology.

Medicines and Guidelines

There are a number of effective treatments that can help prevent fractures and increase bone density.³ These include:

Hormone replacement therapy (HRT), a prescription-only treatment, aims to restore

estrogen to a premenopausal level. In the short term, it is taken to relieve menopausal symptoms, such as hot flashes, night sweats, and vaginal dryness. Small doses over several years also reduce osteoporosis. Some women may experience breast tenderness and nausea as side effects of the treatment. HRT can also increase the risk of developing breast and uterine cancer, but the risk remains low.

There are more than 30 forms of HRT available in pills, patches, under-the-skin implants, or gels.

Bisphosphonates are nonhormonal medicines that block the breakdown of bone. These include Fosamax (alendronate), Didronel® (etidronate), Boniva® (ibandronate), Aredia® (pamidronate), Actonel® (risedronate), Skelid® (tiludronate), and Zometa® (zoledronic acid).

Selective estrogen-receptor modulators (SERMs) are synthetic hormone replacements that work by copying the effects of estrogen on the bones. This type of drug reduces the risk of osteoporosis and heart disease but appears not to increase the risk of breast or endometrial cancers. The SERM currently available for osteoporosis is Evista® (raloxifene).

Calcitonin is a hormone made by the thyroid gland that blocks the action of the cells that are responsible for breaking down bone. It is available in injection form and as a nasal spray.

Parathyroid hormone (Forteo/teriparatide) regulates calcium and phosphate metabolism in the bone and kidney.

It is evident that, when compared with the current U.S. system of reimbursement, the cost-effectiveness limitations imposed by the PBAC in Australia, in particular, limit the use of osteoporosis treatments for the prevention of osteoporosis. IMS can find no evidence of PBS inclusion of any drugs for the prevention of osteoporosis. It appears that PBS lists medicines only for the treatment of patients who have already suffered bone fractures due to osteoporosis.

Patient Impact

The drugs included in this analysis were Fosamax (alendronate), Actonel (risedronate), and Forteo (teriparatide).

The Australian guidelines are compared with the U.S. guidelines for these products in Table 1. The restrictions shown for Actonel (risedronate) also apply to Evista (raloxifene), which is indicated in the United States for the prevention and treatment of osteoporosis but only for established postmenopausal osteoporosis in Australia.

It was not possible using the IMS MIDAS Prescribing Insights™ database to determine whether these products were being prescribed as preventive measures or as a treatment for osteoporosis in the U.S. retail setting. U.S. guidelines⁴ currently allow Fosamax (alendronate) and Actonel (risedronate) to be prescribed for both prevention and treatment of osteoporosis.

According to FDA-approved labeling, Forteo (teriparatide) should be prescribed as a treatment for only postmenopausal women with a high risk of bone fracture or for those who actually have the disease. It is likely that Forteo (teriparatide) is being prescribed in line with labeled indications for two main reasons: the current formulation is a daily injection administered by a pen that must be kept refrigerated, and it is considered relatively expensive.

Examination of co-prescribing data indicated that, despite the findings of a recent *The New England Journal of Medicine* study⁵ that showed that Forteo (teriparatide) in combination with Fosamax (alendronate) reduced the effectiveness of Fosamax (alendronate) alone, Forteo (teriparatide) has been prescribed with Fosamax (alendronate) and Actonel (risedronate) in low numbers. The maximum number of patients that this finding could equate to have been removed from the data to prevent double counting.

Table 1

U.S. and Australian Prescribing Indications for Selected Products in the Osteoporosis Market, 2004

International Product	U.S. Prescribing Guidelines, 2004*	Australian Prescribing Guidelines, 2004
Actonel	20-835 For osteoporosis and Paget's disease.	Initial treatment for established osteoporosis in patients with fractures due to minimal trauma. The fracture may have been demonstrated radiologically, and the year of plain x-ray or CT-scan must be included in the authority application. A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or midportion of a vertebral body relative to the posterior height of that body, or a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body. Continuing treatment for established osteoporosis in patients with fracture due to minimal trauma, where the patient has previously been issued with an authority prescription for this drug.
Forteo	21-318 For the treatment of postmenopausal women with osteoporosis who are at high risk for fracture. These include women with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant of previous osteoporosis therapy, based upon physical assessment. Indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. These include men with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant to previous osteoporosis therapy, based upon physician assessment.	Not available.
Fosamax	20-560 For the prevention and treatment of osteoporosis.	Initial treatment for established osteoporosis in patients with fracture due to minimal trauma.

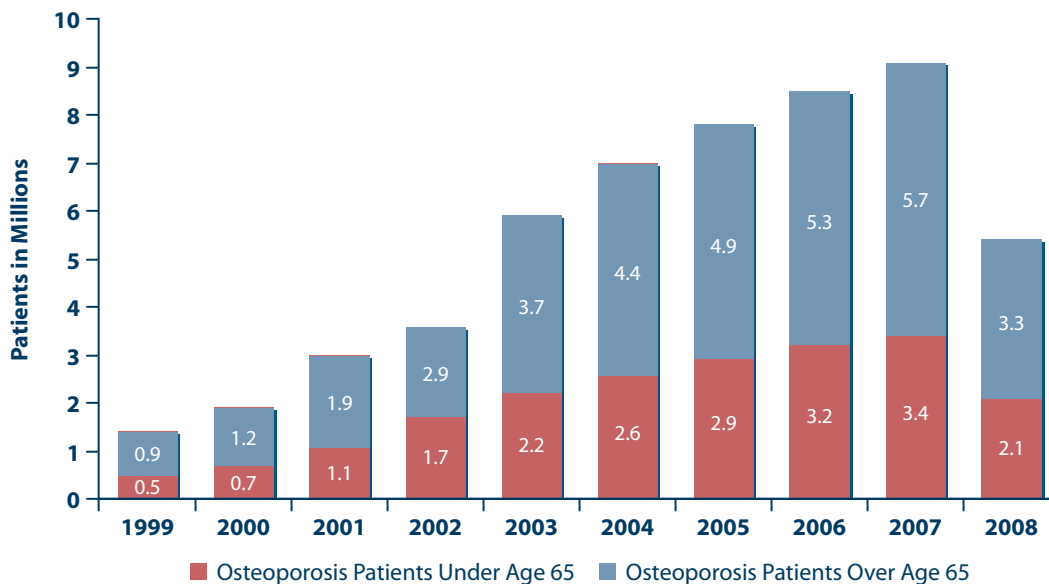
*Source: National Osteoporosis Foundation, *Physician's Guide to Prevent and Treatment of Osteoporosis* (Washington, DC: National Osteoporosis Foundation, April 2003) 37.

Forteo (teriparatide), which is the only product currently available that has been proven to promote the activity of bone-forming cells (osteoblasts) and new bone growth, is not permitted at all under PBAC regulations. The PBAC rejected Forteo (teriparatide) because of uncertainties over the comparative effectiveness of Forteo (teriparatide) over antiresorptive therapy.

IMS believes, based on current literature,⁶ that the U.S. osteoporosis market is underserved. With improved knowledge and diagnostic techniques, there is scope for all three osteoporosis products covered in this project to grow and reach significantly more new patients over the next five years. IMS believes that by 2007, approximately 9.1 million patients in the

Figure 2

Patients Forecast to Be Affected in the United States in the Osteoporosis Therapy Area, 1999–2008



United States with osteoporosis could be affected if the PBAC guidelines are applied in the United States. Patients who are at risk of developing osteoporosis, but have not yet been diagnosed, will be particularly affected under this regime. This is because some osteoporosis therapies are excluded from listing and, therefore, largely not available under the Australia PBS, and those that are listed are available only under much more restrictive conditions; that is, women must first suffer fractures before the treatments are made available to them.

...By 2007, approximately 9.1 million patients in the United States with osteoporosis could be affected if the PBAC guidelines are applied in the United States.

Alzheimer’s Disease

Disease Overview

Alzheimer’s disease is a serious disorder of the brain’s nerve cells, impairing memory and thinking and behavior and leading ultimately to death. An estimated 4.5 million Americans are currently suffering from the disease; this figure is almost double that in 1980.⁷ It is projected that the number of Americans with the disease will continue to grow. These increasing numbers are due to the fact that the greatest risk factor for Alzheimer’s is increasing age, and the longevity of the American population continues to increase.

In 2004, the U.S. direct and indirect cost of caring for individuals with Alzheimer’s was at least \$100 billion, according to estimates by the Alzheimer’s Institute and the National Institute of Aging. In 2004, Alzheimer’s cost American businesses \$61 billion. Of this figure, \$24.6 billion covers Alzheimer’s health care and \$36.5 billion covers costs associated

with those who care for Alzheimer's patients. The average lifetime cost of caring for an individual with Alzheimer's is \$174,000. By 2010, Medicare costs for beneficiaries with Alzheimer's are expected to increase 54.5 percent, from \$31.9 billion in 2000 to \$49.3 billion. Medicaid expenditures on residential dementia care will increase 80 percent, from \$18.2 billion in 2000 to \$33 billion in 2010.

Medicines and Guidelines

The FDA has approved two classes of drugs to treat cognitive symptoms of Alzheimer's disease. The first Alzheimer's medications to be approved were cholinesterase inhibitors. Three of these drugs are commonly prescribed—Aricept® (donepezil), approved in 1996; Exelon® (rivastigmine), approved in 2000; and Razadyne (galantamine), approved in 2001. Cognex® (tacrine), the first cholinesterase inhibitor, was approved in 1993 but is rarely prescribed today because of associated side effects, including possible liver damage. The Australian PBS guidelines are identical for Aricept (donepezil), Exelon (rivastigmine), and Razadyne (galantamine) and are highly restrictive compared with U.S. guidelines.

Namenda (memantine) is a drug approved in October 2003 by the FDA for treatment of moderate to severe Alzheimer's disease. Namenda (memantine) is classified as an *uncompetitive, low-to-moderate affinity, N-methyl-D-aspartate (NMDA) receptor antagonist*, the first Alzheimer's drug of this type approved in the United States. It appears to work by regulating the activity of glutamate storage and retrieval. Glutamate triggers NMDA receptors to allow a controlled amount of calcium to flow into a nerve cell, creating the chemical environment required for information storage.

Excess glutamate, on the other hand, overstimulates NMDA receptors to allow too much calcium into nerve cells, leading to disruption

and death of cells. Namenda (memantine) may protect cells against excess glutamate by partially blocking NMDA receptors.

Patient Impact

The two products examined in the Alzheimer's therapy area were Razadyne (galantamine) and Namenda (memantine). Razadyne (galantamine) is authorized under Australian guidelines, although prescribing is restricted by the requirement for mini-mental tests. Namenda (memantine) is not included in the PBS. The PBAC rejected the submission because of concerns with the extent of the clinical effect and the resulting cost-effectiveness claim. [Table 2]

The PBS guidelines are more restrictive than U.S. guidelines and would impact approximately 400,000 U.S. patients with Alzheimer's were they applied to the U.S. health system. Namenda (memantine) is available for treatment of moderate to severe dementia in the United States, and Razadyne (galantamine) is available without being subject to the restrictions placed on it by the PBS. In particular, the Australian government requires a specific score on the "Mini-Mental State Exam" (MMSE), a test of cognitive ability, before it will provide reimbursement. It also limits coverage of the medicine to six months of treatment unless the patient shows "significant improvement."

In the United States, the MMSE test is widely used, but physicians and patients generally have more flexibility in deciding when to begin therapy. In addition, the decision on whether to continue therapy is based on patient satisfaction, which can include maintenance of current mental status and prevention of mental decline.

Using IMS diagnosis information, it is not possible to segment the market by mild, moderate, and severe Alzheimer's disease. This is an issue for the Alzheimer's market where the current U.S. indications specify the severity of

Table 2		
U.S. and Australian Prescribing Indications for Selected Products in the Alzheimer's Market, 2004		
International Product	U.S. Prescribing Guidelines, 2004*	Australian Prescribing Guidelines, 2004
Razadyne	21-224 Mild to moderate dementia of Alzheimer's disease.	Authority required. For initial treatment of mild to moderately severe Alzheimer's disease. Confirmation of diagnosis required by specialist/consultant physician. <i>Application must include result of baseline MMSE. Score must be 10 or above and if over 25—ADAS-Cog score must also be specified. Six months of treatment only is allowed unless significant improvement is shown.</i>
Namenda	21-487 Indicated for the treatment of moderate to severe dementia associated with Alzheimer's disease.	Rejected.

*Sources: J. L. Cummings, J. C. Frank et. al., "Guidelines for Managing Alzheimer's Disease: Part I. Assessment," *American Family Physician* 65, no. 11 (1 June 2002) 2663-2272.

J. L. Cummings, J. C. Frank et. al., "Guidelines for Managing Alzheimer's Disease" Part II. Treatment," *American Family Physician* 65, no. 12 (15 June 2002) 2525-2534

Alzheimer's disease for the products we are examining. However, the indications do not specify how the prescriber should identify the mild, moderate, and severe stages of the disease. It is believed that most patients do not present to a physician with symptoms of dementia until the disease is at a moderate stage. IMS has not currently recorded any co-prescribing of the products in this therapy area.

We believe that the Alzheimer's therapy area is currently unsatisfied. Better diagnostic techniques and the launch of new therapies such as Razadyne (galantamine) and Namenda (memantine) will increase awareness over the next five years. Recently published prevalence estimates are that by 2050 the U.S. population with Alzheimer's disease will have almost tripled to 13.2 million.

IMS estimates that a maximum of 1.6 million Alzheimer's patients could be affected if the United States were to adopt the same system as Australia. [Figure 3] Specifically, Namenda

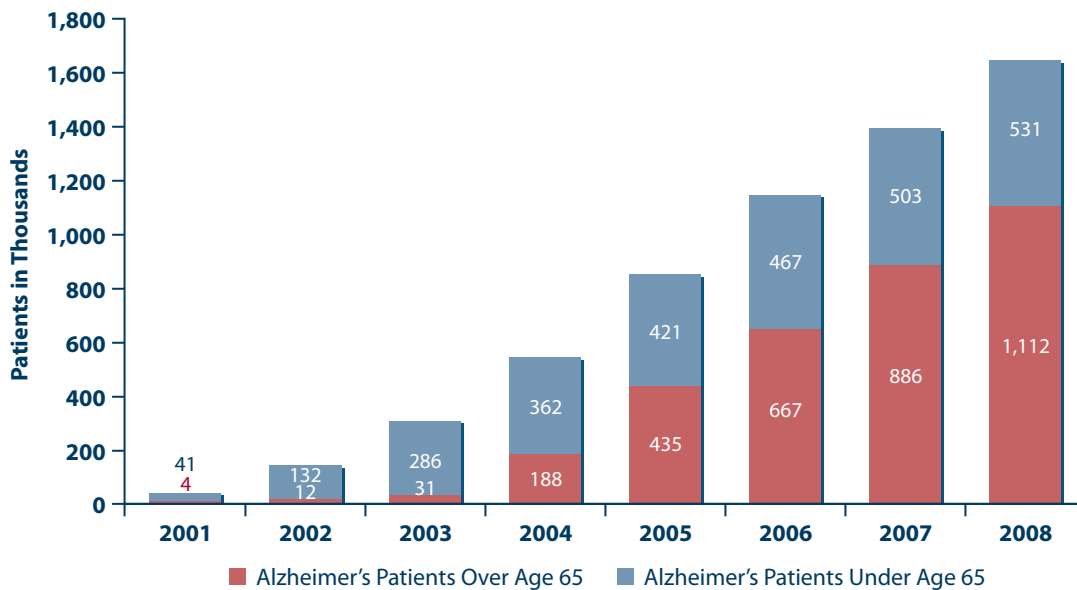
(memantine) would not be covered for Alzheimer's treatment, and Razadyne (galantamine) would be reimbursed only under much more restrictive conditions.

IMS estimates that a maximum of 1.6 million Alzheimer's patients could be affected if the United States were to adopt the same system as Australia.

To date, there have been no recorded instances of these drugs being prescribed in combination. However, as the drugs used in this analysis have been proven to be effective combined together and for the same indications, it is likely that this estimate includes some double counting. These products are very new to the market, and it is not possible at this time to estimate how large this could be. Also, the estimates of patient age for these products are made using the current

Figure 3

Patients Forecast to Be Affected in the United States in the Alzheimer's Therapy Area, 2001–2008



data available, which relate to a small number of prescriptions in the retail sector only. It is likely that there will be a more equal split of prescribing between the under- and over-65-year-olds as these products mature and diagnostic techniques improve.

Orphan Drugs

Disease Overview

Essential Thrombocythemia (ET) is a myeloproliferative disease. Myeloproliferative diseases (MPDs) are diseases in which one or more of the types of cells that make up the blood are being overproduced or overproliferated. Platelets are a special type of cell found in the blood that help it clot to stop bleeding.

Although platelets normally perform this very important function without causing health problems, people with MPDs, such as ET, are at increased risk of medical problems because they have an abnormally high number of platelets in their blood.

ET is characterised by platelet counts greater than 400,000. Other MPDs include Polycythemia Vera (PV), Agnogenic Myeloid Metaplasia (AMM), Secondary Myelofibrosis (MF), and Chronic Myelogenous Leukemia (CML). These conditions share similar features and are classified according to the cell type that shows the greatest involvement. There is a great deal of overlap between the conditions, and a transition from one to another is common. The published incidence of ET varies from 0.1–2.4/100,000.

Pulmonary arterial hypertension (PAH) is another rare orphan status condition. PAH includes conditions where the mean pulmonary arterial pressure is >25 mmHg at rest and >30 mmHg with exercise. Primary pulmonary hypertension has an estimated incidence of two cases per million people. PAH associated with other diseases, also called secondary PAH, shows a higher incidence. In the early stages of PAH, symptoms include breathlessness, palpitations, fatigue, and a pounding

heart. As PAH progresses, ankle edema and, later, right-sided congestion (elevated jugular venous pressure, ascites, hepatomegaly, and peripheral edema) occur.

Medicines and Guidelines

Agrylin (anagrelide) is the only therapy currently indicated to treat thrombocythemia.

Four drugs are approved in the United States to treat PAH:

Flolan® (epoprostenol) helps to open up constricted blood vessels. Flolan (epoprostenol) has not yet received approval in Australia.

Tracleer® (bosentan) is an endothelin receptor antagonist. It works by decreasing the stiffness of the blood vessels as well as widening them to allow blood to flow more easily.

Remodulin® (treprostinil sodium) helps to dilate arteries and to prevent blood clot formation.

Ventavis® (iloprost) is an orally inhaled prostaglandin and works by dilating the blood vessels and prevents blood clot formation.

Patient Impact

This study includes the analysis of two orphan drugs for different therapy areas. Currently, IMS does not have an age breakdown for one of these products.

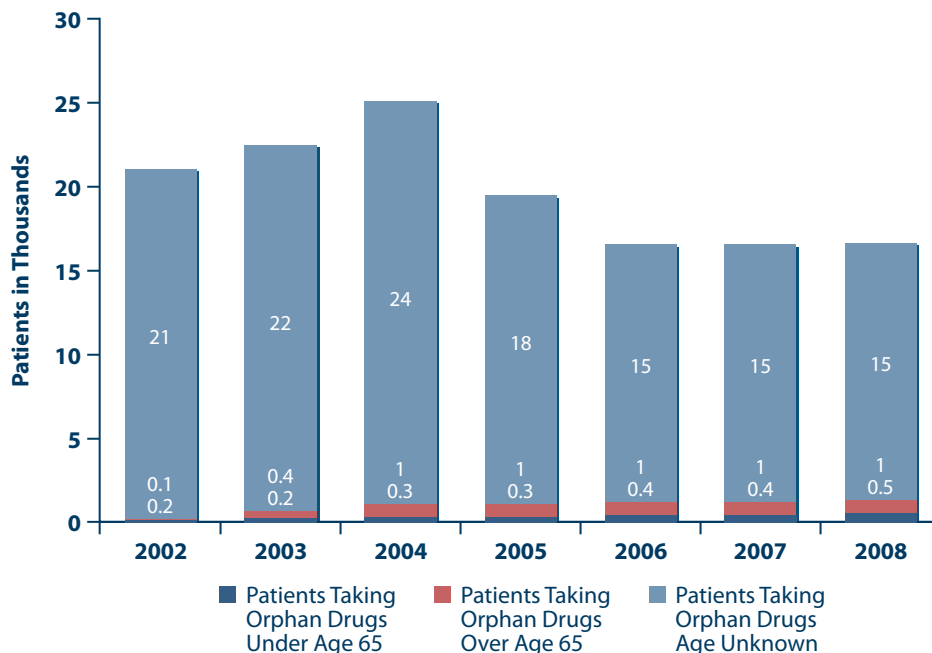
While Tracleer (bosentan) is now reimbursed on some level in Australia, the prescribing guidelines are very restrictive involving three clinical tests.

Agrylin (anagrelide) was rejected by PBAC. It was deemed that Agrylin (anagrelide) reduced platelet count and symptom rate regardless of baseline platelet levels. Therefore, PBAC rejected Agrylin (anagrelide) on the grounds that “platelet count thresholds for initiating and continuing treatment may not be justified.”

Table 3 U.S. and Australian Prescribing Indications for Selected Products in the Orphan Drug Market, 2004		
International Product	U.S. Prescribing Guidelines, 2004	Australian Prescribing Guidelines, 2004
Agrylin	20-333 For patients with thrombocythemia secondary to myeloproliferative disorders. To reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombo-hemorrhagic events.	Rejected.
Tracleer	21-290/S-001 For the treatment of pulmonary arterial hypertension in patients with WHO Class III or IV symptoms. To improve exercise ability and decrease the rate of clinical worsening.	Indicated for patients with WHO Class III and a mean right arterial pressure of eight mmHg or less or WHO Class IV. Not PBS subsidized for patients with pulmonary hypertension secondary to interstitial lung disease with scleroderma, where the total lung capacity is less than 70% of that predicted. Written submission to use Tracleer must include the results of a right heart catheter, ECHO, and six-minute walk test or an explanation as to why these tests could not be performed. Treatment applications must be repeated every six months.

Figure 4

Patients Forecast to Be Affected in the United States in the Orphan Drug Area, 2001–2008



In total, approximately 25,000 people with orphan diseases would have difficulty being treated if these guidelines were implemented in the United States. This is equivalent to 66 per cent of the total population with these diseases.

5. CONCLUSION

Australia is one of the few countries in the world that employs a cost-effectiveness requirement to decide whether to grant reimbursement for new medicines. This report examined seven medicines for which Australia had employed cost-effectiveness analysis and decided to deny reimbursement listing or grant reimbursement listing, but with restrictions not in place in the United States.

These seven medicines are presently used to treat millions of patients in the United States for Alzheimer’s, osteoporosis, and rare

disorders. These patients would face significant hurdles in gaining access to these medicines if a cost-effectiveness standard similar to Australia’s was applied broadly to deny reimbursement for these therapies in the United States. Many more patients would be affected similarly if this analysis addressed more medicines for which cost-effectiveness was cited as a factor in denying reimbursement listing in Australia.

In the United States, patients value access to innovative therapies for serious and life-threatening diseases and conditions like Alzheimer’s disease and osteoporosis. Policymakers carefully should weigh the potential impact on access to innovative medicines when deciding whether to apply cost-effectiveness standards similar to those used in Australia before making medicines available to patients.

6. REFERENCES

1. N. S. B. Rawson, “Time Required for Approval of New Drugs in Canada, Australia, Sweden, the United Kingdom and the United States in 1996–1998,” *Canadian Medical Association Journal* 162, no. 4 (22 February 2000): 501–504.
2. P. J. Neumann, “Evidence-Based And Value-Based Formulary Guidelines,” *Health Affairs* 23, no. 1 (2004): 124–134.
3. S. Khosla, “Parathyroid Hormone Plus Alendronate—A Combination That Does Not Add Up,” *New England Journal of Medicine* 349, no. 13 (25 September 2003): 1277–1279.
4. National Osteoporosis Foundation, *Physician’s Guide to Prevention and Treatment of Osteoporosis* (Washington, DC: National Osteoporosis Foundation, 2003).
5. S. Khosla, *op. cit.*
6. U.S. Surgeon General’s Office, “Bone Health and Osteoporosis,” *Surgeon General’s Report* (Washington, DC: U.S. Surgeon General’s Office, 2004.)
7. L. E. Hebert et al., “Alzheimer Disease in the US Population: Prevalence Estimates Using the 2000 Census,” *Archives of Neurology* 60, no. 8 (August 2003): 1119–1122.