

Considerations in Creating a Medicare Part D Formulary

**A guide for prescription drug plans to
appropriate selection of therapeutic agents**

HIGHLIGHTS

Concepts

- Strategies for Developing a Successful Medicare Part D Formulary

Examples

- Antidementia Agents: What Is Important in This Class
- The Role of Tumor Necrosis Factor Inhibitors in Medicare Part D Formularies
- Bisphosphonates: Providing Strength to a Significant Class

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INTRODUCTORY MESSAGE

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It's All About Access

Having had the opportunity to spend a year at the Centers for Medicare and Medicaid Services as a Health Policy Scholar working on the Medicare Modernization Act, I can say that the cornerstone of the Medicare prescription drug benefit is simple: access. Access to medications is critical to all who are touched by Medicare Part D. Beneficiaries want increased access and are hopeful that this access will result in reduced out-of-pocket expenses. Prescribers want access to medications of their choosing. Prescription drug plans (PDPs), the groups managing this benefit, want to control access to assure the financial viability of their programs while making medications accessible enough to attract enrollment. Medicare Advantage plans want to promote access to medications that can reduce hospitalization and other expenditures.

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This access will come through three channels designed by each Part D plan: transitioning plans, appeals process, and formulary design. Because *optimum* access does not mean *unlimited* access to medications, each channel needs to be constructed carefully to achieve optimum access. "Transitioning plans" refers to requirements that Part D plans provide a transition from uncovered to covered medications. Similarly, plans need an appropriate appeals process that allows prescribers to argue that a nonformulary medication needs to be covered for specific patients because of unique circumstances.

But the primary channel will be the formulary. Formulary designs that utilize prior authorization, restricted access, and exclusions are required to achieve best outcomes on both clinical and financial bases. Medications such as those identified using the Beers criteria for determining potentially inappropriate medications for the elderly are best restricted, if not totally excluded, to avoid adverse events. Prior authorization is one of the best systems available to ensure that the right medication is getting to the right patient; inappropriate use of medications (such as Cox-2 inhibitors) is an example. Finally, medications that are grossly inferior to others in the same class should be excluded. Given our limited space, and because of the critical role that formularies play in achieving ideal access to medications, formulary design is the focus of this publication.

Achieving the ideal formulary will be challenging. It will come only with hard work by a dedicated pharmacy and therapeutic committee. These articles can be used as a starting point — an example of the information P&T committees will need — to begin to make appropriate decisions about formulary inclusions and design.

In the end, the Medicare prescription drug benefit is all about access. Achieving optimum outcomes, however, will be anything but simple.

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Strategies for Developing a Successful Medicare Part D Formulary

RICHARD G. STEFANACCI, DO, MGH, MBA, AGSF, CMD

Since the creation of Medicare in 1965, drug therapies have played an ever-increasing role in patient care (Heffler 2004). Outpatient therapies for diabetes, hypertension, lipid disorders, depression, and many other diseases have improved health outcomes and resulted in reduced hospitalization and ER visits. Outpatient drug therapies have become a major part of care plans for clinicians in every medical discipline.

Although outpatient prescription drugs for acute and chronic conditions are covered routinely by most private and Medicaid payers, Medicare has paid for drugs only during acute inpatient stays and when administered by a physician. Medicare beneficiaries have relied on a patchwork of outpatient drug coverage from employer or retirement benefit plans or from supplemental plans, or they have gone without drug coverage. With the passage of the Medicare Prescription Drug, Improvement and Modernization Act of 2003 (MMA), beneficiaries will be offered a comprehensive drug benefit beginning Jan. 1, 2006. This benefit is commonly referred to as the Medicare Part D benefit (CMS 2005a, 2005b).

Types of coverage

The MMA legislation created or enhanced four avenues for coverage of outpatient drugs for beneficiaries:

Subsidies for employers to continue retiree drug coverage. The subsidy will be a tax credit of 28 percent of the employer cost of providing such coverage and is intended to encourage employers who currently offer a retirement drug benefit to continue to do so. This subsidy will average \$668 per retiree per year.

Medicare Advantage Prescription Drug Plans. Medicare Advantage (MA) plans that offer the equivalent of Medicare Part A and Part B coverage also must offer an add-on drug benefit (for an additional monthly premium) to their Medicare members that is actuarially equivalent to the benefit under Part D. These MA-PD plans will be paid subsidies for low-income beneficiaries, high-cost beneficiaries, and patients in long-term care.

Prescription drug plans (PDPs). These are new capitated plans that will contract with the Centers for Medicare and Medicaid Services (CMS) to provide regional or national drug coverage to Medicare beneficiaries. These at-risk PDPs are free to develop formularies and cost-sharing mechanisms, but their formularies and coverage must be actuarially equivalent to the basic drug benefit described

in the law. PDPs will bid a per-member annual cost and will be paid a fixed rate for providing a defined drug benefit. The PDPs are at risk for the cost of providing benefit to their members, and, like MA-PD plans, will receive subsidies for low-income and high-cost beneficiaries.

Fallback PDPs. These plans bear no risk for beneficiary drug costs, but provide the administration and delivery of the drug benefit package described in the law for an administrative fee only. In this case, CMS bears the financial burden of the drug cost itself. CMS regards this as a last resort for providing a drug benefit in regions where there is inadequate coverage from the three methods discussed above. CMS intends to work with payers and pharmacy benefit managers (PBMs) to do everything possible to ensure successful bidding and implementation of the MA-PDPs and at-risk PDPs, so that the number of beneficiaries covered by fallback PDPs is minimal.

The primary financial motivation varies among plan types (Table 1, page 4). The employer subsidy will encourage companies that already have contracted for retirees' drug benefits to continue them. The MA-PDP has an incentive to encourage drug use where it reduces other medical costs, because the plan is at risk for medical and drug costs. The at-risk PDP has a financial incentive to minimize only drug use, because the PDP will not realize the benefit from any trade-off between drug and medical costs. Finally, fallback PDPs will behave like typical PBMs in the private sector, taking no insurance risk and administering the benefit for a transaction-based fee only.

Implementation and drug benefit structure

To encourage robust participation and competition, CMS has organized the nation into 34 regions. PDPs

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must bid to cover at least one region but may bid on multiple regions. To provide adequate choice, CMS will offer a fallback PDP in regions without at least two at-risk PDPs.

The implementation of the new Medicare drug benefit is on a very short timeline (Table 2), considering that many details must be worked out in fewer than seven months. Although MA plans exist and can use their actuarial experience to structure their bids, there are no players in the at-risk arena for beneficiaries. Potential bidders will have to bid financial terms for specific regions at the same time they are negotiating formulary rules for their proposed plans.

The basic drug benefit design specified in the MMA is depicted in Table 3 and Figure 1 (page 6). The beneficiary is responsible for a \$250 deductible. After the deductible is paid, the beneficiary coinsurance is 25 percent, up to a specified limit (\$2,250 in total drug expenditure). Beyond this limit, there is a coverage gap (the “donut hole”) in which the beneficiary is fully responsible for prescription drug costs until \$5,100 in total drug expenditure has been reached (the equivalent of \$3,600 in out-of-pocket spending). Thereafter, CMS-subsidized “catastrophic coverage” features a 5 percent patient copayment. This unusual benefit design was a political compromise that provided coverage for both “typical” beneficiaries with a median drug expenditure of \$2,500 and for seriously ill people with extremely high drug expense — while keeping cost estimates within negotiated spending limits. The basic benefit also provides CMS-subsidized cost sharing for low-income beneficiaries and dual eligibles.

Role of P&T committee

The MMA allows plans to strike a balance between expansiveness of coverage and cost containment. Plans are encouraged to use formularies, copayment tiering, prior authorization and other pharmacy benefit management tools in their designs. CMS was told in the MMA legislation to use U.S. Pharmacopeia to develop model formulary categories and classes, but has said that plans are free to propose their own formularies and management tools as long as they adhere to “widely recognized best practices.” CMS will review each proposed PDP or MA-PDP bid for potentially discriminatory practices that might limit care to patients with high-cost conditions. To that end, CMS will review the plan’s pharmacy and therapeutics (P&T) committee structure and role, formularies, and its use of drug-benefit management tools.

CMS will use four principles to guide these reviews. It will (1) compare proposed plans to existing “widely recognized best practices” of plans that now provide pre-

TABLE 1 Types of Medicare prescription plans

<i>Medicare prescription plan</i>	<i>Primary motive of plan</i>
CMS-subsidized employer-based benefit	Continuation of contracted benefit with reduced annual costs
Medicare Advantage prescription drug plans (MA-PDP)	Value of drug therapy in overall patient care, including reduced medical costs
Fallback prescription drug plans	Fixed administrative fees
At-risk prescription drug plans	Drug cost minimization

CMS=Centers for Medicare and Medicaid Services.

scription benefits to Medicare beneficiaries, (2) ensure that proposed plans provide access to medically necessary drugs, (3) allow flexibility for plans to design benefits that “promote real beneficiary choice while protecting beneficiaries from discrimination,” and (4) encourage plans to use administratively efficient processes.

With respect to reviews of plans’ proposed P&T committee structure and role, CMS provides guidance in a number of areas. P&T committees must have the power to make binding decisions to place a drug on formulary. P&T committees will approve therapeutic classes on an annual basis and will meet quarterly to review newly approved drugs and indications. More than half the makeup of a P&T committee must include actively practicing physicians and/or pharmacists. In addition, P&T committees must include at least one physician and one pharmacist with experience and training in caring for the elderly or the disabled, as well as being independent from the Part D plan and pharmaceutical companies.

CMS’s formulary-review process will incorporate best practices from the private sector, Medicaid, and plans that participate in the Federal Employees Health Benefits Program. Formularies will be checked for inclusion of a range of drugs in a broad distribution of therapeutic categories and classes, consideration of specific drugs, and tiered-cost-sharing and drug-utilization-management strategies. Where CMS feels a proposed plan differs from common management practices, it will require written clinical justification from the bidding plan.

Six guiding principles

CMS will use six principles to determine the adequacy of the proposed formulary of a potential Part D bidder:

1. *Key drug types.* CMS will review formularies for at least one drug in each of the 146 *key drug types* identified by USP. Plans may present a reasonable clinical justification for not including a medication in a type.

2. *Risk-adjustment data.* CMS will use Part D risk-adjustment data to assess whether a formulary includes drugs most commonly used by the Medicare population and that are reflected across the Drug Hierarchical Con-

TABLE 2 Part D implementation timeline

Plan application process (left of center column)

When application, formulary, and bid processes are completed, a plan is awarded a contract.

Application	Formulary	Bid	Date	CMS action	PDPs/beneficiaries
Feb. 18 Nonbinding "intent to apply"			Q1 2005	CMS provides formulary guidance	PDPs begin risk modeling and application process
Mar. 23 Deadline for application	Mar. 28 Begin submitting			CMS holds workshops for potential PDP bidders	
May/June-- Eligibility determination	Apr. 18 Deadline May 16 Approval	May 20 Begin submitting June 6 Deadline	Q2 2005		MA-PDP and at-risk PDP plans submit bids to CMS Bidders submit proposed formularies and copay- ment tiers for CMS review
July 16-- Last day for favorable redetermination		July 24 Preliminary approvals Aug 2 National cov- erage premium Sept. 2 Approvals	Q3 2005	Sept. 2 CMS awards at- risk PDP and MA-PDP contracts; CMS begins auto- enrollment of dual eligibles into Part D	
			Q4 2005	Oct. 15 CMS sends plan information to beneficiaries	Nov. 15 Beneficiaries begin enrollment in PDPs
			Q1 2006	Jan. 1 CMS begins paying low-income and catastrophic subsidies to PDP plans; CMS-sponsored drug discount card ends	Jan. 1 Plan benefit year begins
			Q2 2006		May 15 Part D open- enrollment period ends

CMS=Centers for Medicare and Medicaid Services; MA=Medicare Advantage; PDP=prescription drug plan;Q=quarter.
SOURCE: HSC 2005

dition Categories (DHCC) used to determine Medicare risk adjustment.

3. *Treatment guidelines.* CMS will analyze formularies to determine whether appropriate access is afforded to drugs, as addressed by widely accepted national treatment guidelines for 26 common conditions, including dementia, rheumatoid arthritis, and osteoporosis.

4. *Tier placement.* CMS will analyze formularies' potential effects on access by examining the cost-sharing tier position of the 40 drug classes most commonly prescribed among the Medicare population (Table 4, page 7).

5. *Avoid cherry picking.* CMS will review tier placement to ensure that a formulary does not discourage enrollment of certain beneficiaries by placing drugs on higher

TABLE 3 Medicare Part D beneficiary cost-sharing structure

Income level*	Premium	Deductible	Cost sharing		
			Up to \$2,250 [†]	\$2,251–\$5,100 [†]	Over \$5,100 [†]
Dual eligibles ≤100% FPL	\$0	\$0	\$1 generic \$3 brand	\$1 generic \$3 brand	\$0
Dual eligibles >100% FPL	\$0	\$0	\$2 generic \$5 brand	\$2 generic \$5 brand	\$0
<135% FPL	\$0	\$0	\$2 generic \$5 brand	\$2 generic \$5 brand	\$0
135%–150% FPL	Income-prorated, up to \$35	\$50	5% coinsurance	5% coinsurance	\$2 generic \$5 brand
>150% FPL (See Fig. 1)	Est. \$35/month	\$250	25% coinsurance	100% coinsurance	5% coinsurance

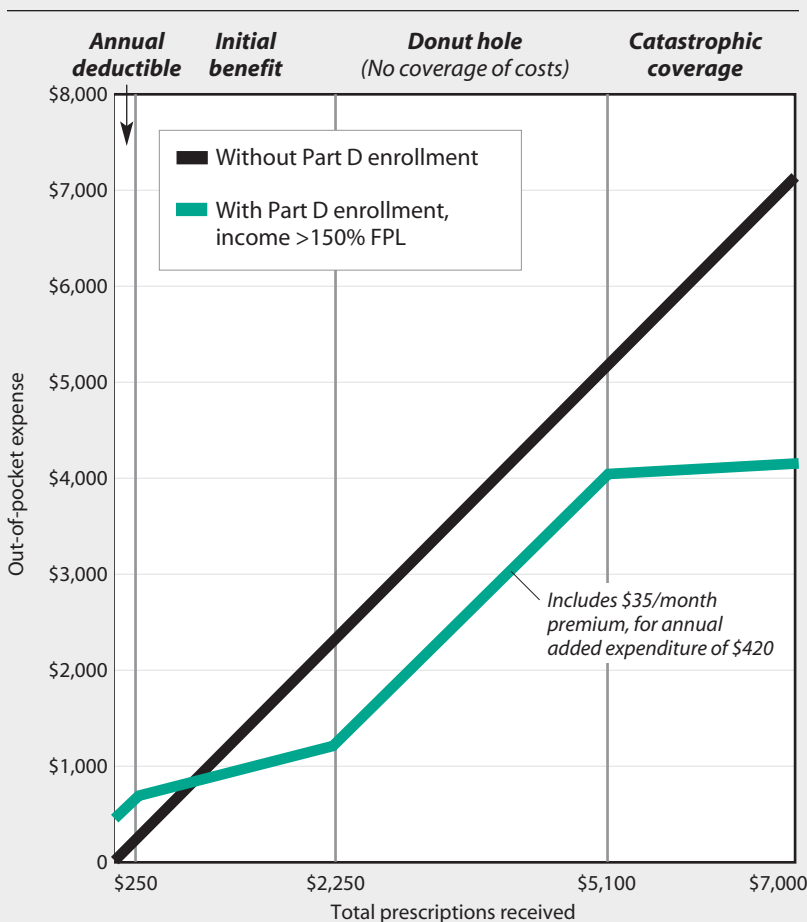
*FPL in 2005 is \$9,570/individual.

[†]In total drug expenditure.

FPL=federal poverty line, PDP=prescription drug plan.

SOURCE: KFF 2005

FIGURE 1 Comparison of out-of-pocket spending, with and without Part D benefit



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tiers in the absence of commonly used therapeutically similar drugs in more preferred positions.

CMS recommends that when Part D plans develop cost-sharing tiers, Tier 1 should be considered the lowest cost-sharing tier available, with higher cost-sharing in subsequent tiers. CMS also notes, for point of reference, that Medicaid preferred-drug lists generally place a product in higher tiers only when drugs that are therapeutically similar are already in more preferable formulary positions.

6. *Choice of medications.* CMS expects that best-practice formularies will contain “a majority” of drugs within the following six therapeutic classes:

- Antidepressants
- Antipsychotics
- Anticonvulsants
- Antiretrovirals
- Immunosuppressants
- Antineoplastics

CMS will check that beneficiaries being treated with these classes have uninterrupted access to all medications in those respective classes through formulary inclusion, utilization management tools, or exceptions processes.

Seven additional strategies

Part D plans can increase the chances that their proposed formularies will be acceptable to CMS by paying attention to seven specific areas:

1. *Safety.* Drugs that have published data on safety and efficacy in the elderly should be given preference over those without elderly-specific data. In a recent paper in the *Journal of the American Geriatric Society*, Beers and Stefanacci noted, “In geriatrics, [formulary] considerations are far more complex. For [these] patients, we must consider age, sex, comorbidities (all of the many of them), other drugs being taken (seven on average), renal function, ability to follow scheduling regimens, ability to swallow pills, and even ability to pay” (Beers 2005).

2. *Competitive offerings.* A formulary should reflect the common managed care and Medicaid formularies in the bidding area. CMS will not look kindly on formularies that offer Medicare beneficiaries fewer choices and options than their managed care neighbors have.

3. *Brand-name products.* Include appropriate branded therapies in similar fashion to regional managed care and Medicaid formularies. Restricting the elderly mostly to generics, when other formularies in the same region do not, could affect the doctor-patient relationship by disrupting prescribing patterns—a potential consequence that could raise a red flag with CMS.

4. *Now playing.* Include drugs provided to beneficiaries through the Medicare Replacement Drug Demonstration, begun in 2004. CMS selected these therapies to provide early Part D benefits to beneficiaries. Table 5, on page 9, lists drugs authorized by CMS for the demonstration (CMS 2005b). These products can replace Part B drugs administered in clinics and hospital outpatient departments. (The demonstration, authorized by Section 641 of the MMA, continues through Dec. 31, 2005.)

5. *Multiple indications.* Include products that have multiple indications, so that a given drug can meet the needs of multiple medical conditions.

6. *Familiarity.* Include market-leading therapies. This is in keeping with the concept that CMS will be more likely to favor formularies that provide beneficiaries with choices that are available to other plans’ beneficiaries.

7. *Cost-effectiveness.* Products shown in published pharmacoeconomic studies to be cost-effective over competing therapies should be preferred over those without such data.

Off-formulary exceptions

A CMS-developed protocol has established standards for coverage determinations when an enrollee or a physician requests a product not on a plan’s formulary. The appeal processes developed by CMS exist within the plan and, if needed, beyond the plan with appeals to independent review entities (Figure 2, page 8).

Utilization management

CMS will review drug-benefit management tools, evaluating them in the context of industry standards and appropriate guidelines from such organizations as the National Committee on Quality Assurance, the Association of Managed Care Pharmacists, and the National Association of Insurance Commissioners. CMS will examine use of such practices as drug-utilization review (DUR), prior authorization (PA), step therapy, and quantity limits. CMS expects that these tools will be used in a fashion consistent with their application to existing formularies. Where a plan may fall outside of best practices, the plan will be asked to provide a reasonable justification.

CMS expects plans to use policies and procedures currently in place in their commercial business, including concurrent, prospective, and/or retrospective utilization review. DUR should assure appropriate access and guard against inappropriate or dangerous utilization of prescription medications. CMS will require standardized reporting from Part D plans on denials, reconsideration and appeals, and exceptions processes, and it will use these

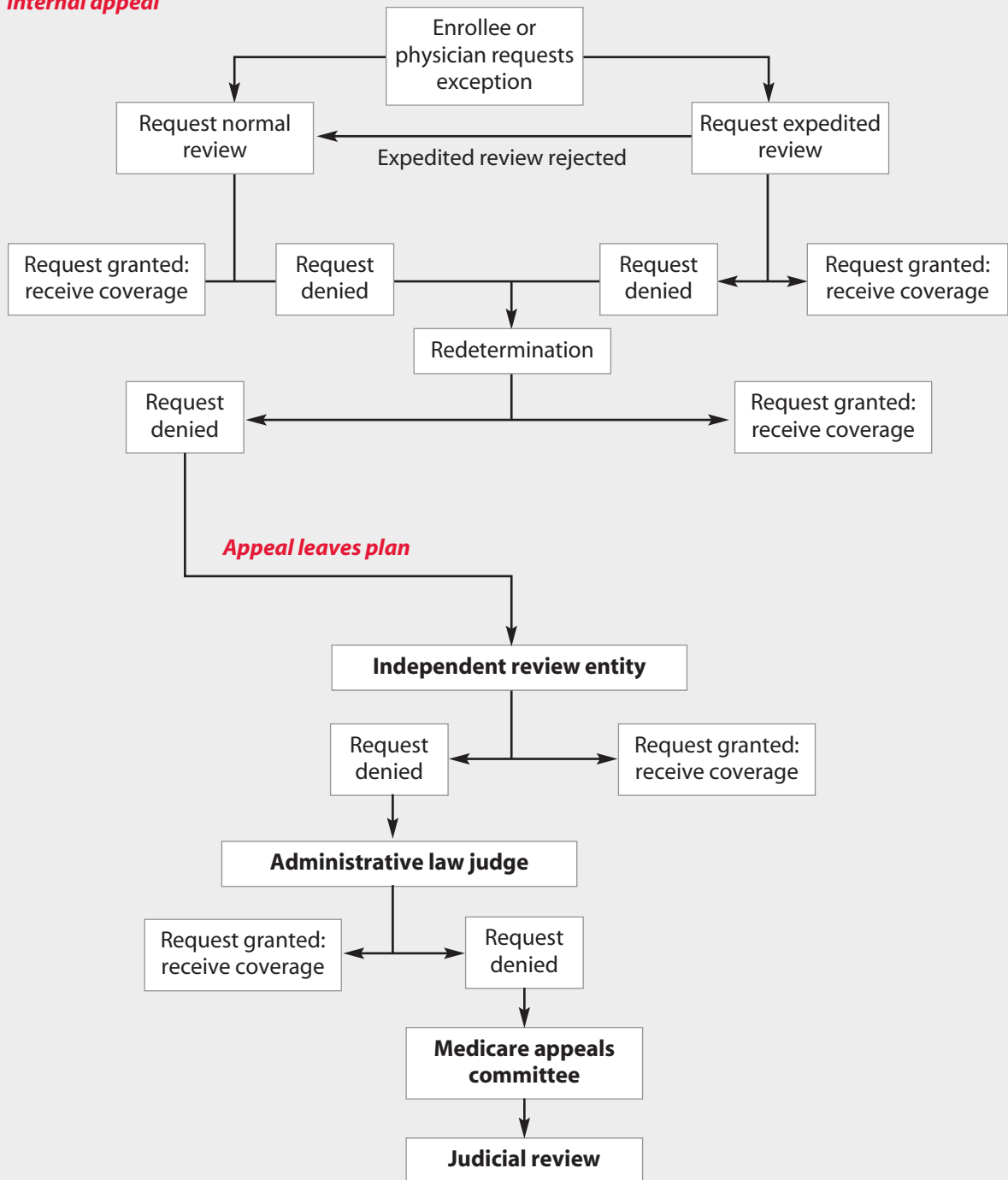
TABLE 4 Most commonly prescribed classes

Angiotensin-converting enzyme (ACE) inhibitors	Corticosteroids	K-sparing diuretic/thiazide diuretic
Alpha blockers	Cox-2 inhibitors	Ophthalmic prostaglandins
Angiotensin receptor blockers	Estrogen replacement	Proton-pump inhibitors
Anticoagulants	Gamma-aminobutyric acid	Quinolones
Antigout	Leukotriene modifiers	Sedatives
Atypical antipsychotics	Long-acting beta agonist/ inhaled corticosteroid	Selective estrogen-receptor modifier
Beta blockers	Loop diuretics	Short-acting beta agonists
Biguanides	Nitrates	Selective serotonin reuptake inhibitors
Bisphosphonates	Nonsedating antihistamines	Statins
Calcium channel blockers (CCB)	Opioids	Sulfonyleureas
CCB/ACE inhibitor	Opioid/analgesic	Thiazide diuretics
Cardiac inotropes	Platelet aggregation inhibitors	Thiazolidinediones
Cholinesterase inhibitors	Potassium (K)	Thyroid replacement
		Tricyclic antidepressants

FIGURE 2 Time frame for coverage decisions

The time frame was reduced considerably when the final rule unified the time frame for drug-benefit and payment-coverage determination.

Internal appeal



SOURCE: HSC 2005. Used with permission.

TABLE 5 Drugs covered under the Medicare Replacement Drug Demonstration

<i>Demonstration-covered indication</i>	<i>Drug/biologic compound name (trade name)</i>
Acromegaly	Pegvisomant (Somavert)
Ankylosing spondylitis	Etanercept (Enbrel)
Cytomegalovirus retinitis	Valganciclovir HCl (Valcyte)
Hepatitis C	Pegylated interferon alfa-2a (Pegasys)
	Pegylated interferon alfa-2b (PEG-Intron)
Multiple sclerosis	Glatiramer acetate (Copaxone)
	Interferon beta-1a (Rebif, Avonex)
	Interferon beta-1b (Betaseron)
	Repository corticotropin injection (H.P. Acthar Gel)
Paget's disease	Alendronate (Fosamax)
	Risedronate (Actonel)
Postmenopausal osteoporosis ¹	Calcitonin-nasal (Miacalcin Nasal)
	Risedronate (Actonel)
	Alendronate (Fosamax)
	Raloxifene HCl (Evista)
Psoriasis	Efalizumab (Raptiva)
	Etanercept (Enbrel)
Psoriatic arthritis	Etanercept (Enbrel)
Pulmonary hypertension	Bosentan (Tracleer)
Rheumatoid arthritis	Adalimumab (Humira)
	Anakinra (Kineret)
	Etanercept (Enbrel)
Secondary hyperparathyroidism	Doxercalciferol (Hectorol)
Anticancer drugs	
Breast cancer (stage 2–4 only)	Anastrozole (Arimidex)
	Exemestane (Aromasin)
	Letrozole (Femara)
	Tamoxifen (Nolvadex)
	Toremifene (Fareston)
Chronic myelogenous leukemia	Imatinib mesylate (Gleevec)
Cutaneous T-cell lymphoma	Bexarotene (Targretin)
Epithelial ovarian cancer	Altretamine (Hexalen)
Gastrointestinal stromal tumor	Imatinib mesylate (Gleevec)
Hemorrhagic cystitis induced by ifosfamide ²	Mesna (Mesnex)
Multiple myeloma	Thalidomide (Thalomid)
Non-small cell lung cancer	Erlotinib HCl (Tarceva)
	Gefitinib (Iressa)

¹ Patient must be homebound. ² Prophylactic agent.
SOURCE: CMS 2005

data for management and oversight activities. Plans should use the data to develop their internal quality initiatives.

CMS will work this year with Part D bidders to refine their proposals to achieve a delicate — and difficult — balance between broad, high-quality drug coverage for Medicare beneficiaries and keeping costs reasonable.

Financing mechanisms

The payments that CMS proposes to make to PDPs are considerably more complex than a simple capitated drug

payment with a few carve-outs. There are four main components of the proposed CMS payments under Part D (CMS 2005c), all of which are designed to decrease plans' risk:

- Basic capitated payments per member per year, with risk adjustment for differing distribution of drug cost by region
- Low-income subsidies to cover premiums and cost sharing of dual eligibles and beneficiaries with in-

comes below 150 percent of the federal poverty line.

- Reinsurance subsidies to cover individuals with catastrophic drug costs (more than \$5,100 per year); for expenses exceeding \$5,100, the beneficiary will pay 5 percent, the plan 15 percent, and CMS 80 percent
- Risk-corridor aggregate payments to part D plans whose overall cost exceeds certain target amounts (in other words, subsidies for unexpectedly high drug costs). These risk corridors go both ways, resulting not only in shared losses, but also shared profits.

CMS has three reasons for wanting to reduce plans' risk. First, drug coverage for the elderly has not been broadly offered to date; where it has, annual-benefit ceilings often have been low. So, PBMs and traditional insurers are unlikely to have adequate actuarial experience that would allow them to make a reasonable bid on a relatively unknown risk. Second, CMS wants to ensure that a large number of plans participate; adequate choice and competition keeps costs to beneficiaries and taxpayers low. Finally, CMS wants to provide catastrophic and risk-corridor payments to ensure that patients with expensive chronic diseases — which are more common in the Medicare population than in the population at large — do not face discrimination through restrictive formularies or other forms of cherry picking by health plans.

Conclusion

The drug benefit is the biggest change to Medicare policy since the creation of Medicare. All stakeholders — beneficiaries, caregivers, clinicians and payers — will benefit if we work together toward a successful outcome.

The extent to which health plans follow the six CMS principles and seven additional considerations outlined in this article can have a significant effect on plans' success with Part D. The articles that follow describe how these principles and considerations may be applied to three key drug types. Careful attention to these details will result in a Part D plan that is attractive to beneficiaries and, thereby, can gain the “critical mass” needed to sustain this program.

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Antidementia Agents: What Is Important in This Class

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Given that increased age is the major risk factor for Alzheimer's disease, the aging and increasing longevity of the U.S. population and its massive Baby Boom cohort make Alzheimer's disease loom large as an immediate and future concern for many. Among those who are going to be affected by this demographic trend are health care providers, policy makers, and financiers, along with the millions of people who have Alzheimer's or are at risk for developing it — as well as the millions more who are entrusted with their care. Even with relatively modest effects from this trend, access to the best available drug treatment will be of increasing interest to all the aforementioned stakeholders.

Alzheimer's disease is the most common type of dementia affecting the elderly in the United States. It is significant because of the toll it exacts in patients, inexorably robbing them of vitality as well as their identity, and because of the tremendous burdens — physical, psychological, and financial — that it imposes on caregivers. At present, about 400,000 new cases of probable Alzheimer's disease are diagnosed annually, and 4.5 million Americans currently are living with this disease (Hebert 2003). A substantial majority of these patients — 3.4 million — are Medicare beneficiaries. This article will discuss antidementia agents that might be included on formularies developed for Medicare beneficiaries in accordance with the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA).

At present, an estimated 10 percent of the U.S. population beyond the age of 65 years has Alzheimer's, but the prevalence rises sharply with increasing age (Evans 1989). Whereas 3 percent of Americans between the ages of 65 and 74 years have Alzheimer's, the prevalence rates for those who are between 75 and 84 years old and those 85 years and older climb to 19 percent and 47 percent, respectively. Differences in annual incidence are just as striking, being 14 times higher for people older than 85

years when compared with those within the age range of 65 to 69 years (Hebert 1995).

Alzheimer's disease cannot be cured, and the overall rate of its progression cannot be prevented; at best, current therapies produce a modest delay (2–7 months) in symptomatic progression. In the absence of medical breakthroughs to prevent or cure Alzheimer's disease, the prevalence and incidence rates for this disease, coupled with demographic trends, point toward a projected 13.2 million Americans having Alzheimer's disease by 2050 (Hebert 2003). Among these people, about 5 million would be ages 75 to 84; 8 million would be 85 or older.

Compared with people of the same age in the general U.S. population, people with Alzheimer's disease have a life expectancy that is considerably shorter, and the survival time for men with Alzheimer's is shorter than that for women with Alzheimer's (Larson 2004). For example, the median life expectancies of 70-year-old men and 70-year-old women diagnosed with Alzheimer's are 4.4 and 8.0 years, respectively, while the median life expectancies for their counterparts in the general population are 12.4 years for men and 15.7 years for women. Disease severity and the presence of comorbid conditions, which are common in the Alzheimer's population, are associated with shorter survival times.

The deposition of beta-amyloid peptide is believed to underlie the pathophysiology of Alzheimer's, but the cause of the disease remains unknown. In early-onset disease, a genetic basis is strongly suspected, but in late-onset disease — which accounts for 90 percent of Alzheimer's cases — evidence for a genetic linkage is murky. The leading hypothesis for the etiology of late-onset Alzheimer's is that beta-amyloid deposition in the brain promotes inflammation that results in neurodegeneration.

Alzheimer's disease is characterized by the insidious emergence of symptoms and gradual progression of the disease (Table 1), notably cognitive decline. During the early stages of disease, subtle deficits in general intelligence and memory may appear (Godbolt 2004). As the disease progresses, people gradually (i.e., over the course of years) become unable to perform activities of daily living (ADL). In this respect, Alzheimer's differs from normal aging, which may be associated with faulty memory and slowed learning skills, but not loss of daily function.

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Initially, functional deficits may be seen in a diminution of time devoted to hobbies and leisure activities. In severe disease, patients are unable to dress or eat without assistance, and they are prone to injury if left unattended.

As cognitive impairment worsens in patients with Alzheimer's disease, personality and behavioral disturbances also may emerge. In the late stages of the disease, these often become so severe that family members' capabilities of providing care for the patient are overwhelmed. As a result of this heavy burden on caretakers, many patients with advanced Alzheimer's disease spend their final months or years in nursing homes; patients with Alzheimer's disease and related disorders are believed to account for half the U.S. nursing home population. Of course, behavioral disturbances, such as aggression and wandering, pose major challenges for nursing home personnel, too.

Clinical diagnosis

A definitive determination of Alzheimer's disease cannot be made except via autopsy. Patients clinically diagnosed with Alzheimer's typically present with a complaint about failing memory. Impaired cognition also may be manifested by difficulties with language, comprehension, and orientation.

A clinical diagnosis of Alzheimer's usually is reached by excluding other causes of memory loss and dementia, such as normal pressure hydrocephalus, vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. Careful questioning of the patient's family members often is important for establishing the gradually progressive nature of the disease.

Except for the use of a noncontrast CT or MR scan initially, to rule out brain neoplasms or subdural hematomas, neuroimaging is not recommended to diagnose Alzheimer's (Knopman 2001). Neuropsychological testing (e.g., the Mini-Mental State Examination [MMSE])

may be employed to assist with the diagnosis. Repeated at intervals of 6 months or so, the MMSE and similar instruments may be useful in detecting gradual decline among patients who present initially with a high level of cognitive function.

Treatment initiation

Early diagnosis of suspected Alzheimer's facilitates early initiation of treatment. Drug therapy should be only one component of a comprehensive multidisciplinary team approach to the care of patients who have Alzheimer's disease.

The chief benefit of pharmacologic treatment for Alzheimer's disease is improved quality of life for patients and caregivers. Although the currently available anti-dementia agents do not extend patients' lives, they may slow disease progression, allowing nursing home placement to be delayed (Geldmacher 2003), owing to a slowing in the rate of cognitive decline and emergence of behavior disturbances.

Treatment options

At present, five agents have received approval from the U.S. Food and Drug Administration for treatment of dementia of the Alzheimer's type (Table 2). Four are cholinesterase inhibitors; one is a modifier of the glutamate pathway. All are indicated only for dementia of the Alzheimer's type. All are administered orally, so Medicare Part B does not cover them. Neither are they included in the Medicare Replacement Drug Demonstration, as they do not serve as replacements for drugs that otherwise can be obtained only in a physician's office.

In the United States Pharmacopoeia (USP) draft model guidelines, released for public comment in August 2004, the therapeutic category now called "Antidementia Agents" was known as "Memory Enhancers — Dementia." Initially, the therapeutic category comprised only two pharmacologic classes, "Parasympathomimetics, Cholinergic" and "Glutamate Pathway Modifiers." The renamed category in the finalized model guidelines, however, contains a third pharmacologic class, "Antidementia Agents, Other," which is noted to include drugs such as ergoloid mesylates. In its written comments submitted to the Centers for Medicare and Medicaid Services (CMS) about the draft model guidelines, the Alzheimer's Association had recommended changing the name of the therapeutic category (on the grounds that the drugs do not enhance memory in normal individuals) but had not requested the inclusion of ergoloid mesylates.

TABLE 1 Stages of Alzheimer's disease

Mild	<ul style="list-style-type: none"> • Normal appearance, generally • Faulty short-term memory • Difficulty with some ADL • Some changes in personality, mood, behavior, motivation
Moderate	<ul style="list-style-type: none"> • Difficulty performing complex tasks • Memory loss apparent • Difficulty with many ADL • Impaired judgment • Psychosis, anxiety, agitation more prominent than in mild stage
Severe	<ul style="list-style-type: none"> • Difficulty with virtually all ADL — loss of independence • Incontinent

ADL=Activities of daily living.

TABLE 2 Therapeutic category: antidementia agents

Pharmacologic class	Pharmaceutical preparations	Initial FDA approval for dementia	FDA-approved indications
Cholinesterase inhibitors	Donepezil (Aricept)	1996	Mild to moderate dementia of the Alzheimer's type
	Galantamine (Reminyl)	2001	Mild to moderate dementia of the Alzheimer's type
	Rivastigmine (Exelon)	2000	Mild to moderate dementia of the Alzheimer's type
	Tacrine (Cognex)	1993	Mild to moderate dementia of the Alzheimer's type
Glutamate pathway modifiers	Memantine (Namenda)	2003	Moderate to severe Alzheimer's disease
Antidementia agents, other	Ergoloid mesylates (Hydergine)	Not approved for dementia of the Alzheimer's type	Age-related dementia

Given the USP's stated intention to develop "well-informed, scientifically based finalized model guidelines," the inclusion of ergoloid mesylates is puzzling. These agents have limited use in the treatment of Alzheimer's disease, because their efficacy has not been established (Olin 2001). Accordingly, in the absence of a solid evidence base, we recommend that P&T committees use incentives that would de-emphasize the use of current medications in this pharmacologic class and encourage appropriate use of agents in the other two classes that have been approved by the FDA for treatment of dementia. Note that according to FDA indications, the drugs in these classes are not interchangeable. Currently, the cholinesterase inhibitors are indicated for treatment of mild to moderate disease, while memantine is indicated for moderate to severe disease.

Cholinesterase inhibitors. The effects attributed to the members of this class are believed to stem from their ability to address a synaptic deficit of the neurotransmitter acetylcholine. Their effectiveness wanes as the number of synapses declines owing to loss of neurons. Tacrine was the first cholinesterase inhibitor to gain FDA approval, but it is seldom used today, due to concerns about hepatotoxic effects and poor adherence stemming from an inconvenient dosing schedule (Table 3, page 14).

The remaining three cholinesterase inhibitors appear to have similar efficacy, with respect to effects on cognitive function (Cummings 2004), but no head-to-head comparisons are available. Patients' response to these drugs is a slowed progression of disease rather than measurable improvement in symptoms. That is, a sign of treatment success may be no change in cognitive status; patients' caregivers need to be advised of this likely outcome in advance, because their expectations may be higher. Rather than being a reason to discontinue therapy, maintenance of the *status quo* is an indication that the drugs are working as intended, stabilizing the patient's

performance and thereby effecting a clinically meaningful alteration in the natural history of the disease (Lopez 2005).

All cholinesterase inhibitors are associated with dose-related cholinergic effects such as nausea and vomiting. These adverse effects tend to be transient; they can be minimized by following the recommended titration schedules and by giving the drug with food. In clinical trials of cholinesterase inhibitors, the number of subjects who discontinued treatment owing to side effects was small. The cholinesterase inhibitors also are associated with few drug-drug interactions — an important consideration in a population where polypharmacy for numerous comorbidities is rife: 95 percent of Medicare beneficiaries with dementia have at least one other chronic condition, and up to 90 percent of patients with Alzheimer's require drug treatment for various neuropsychiatric symptoms.

The cholinesterase inhibitors are approved by the FDA for use in mild to moderate Alzheimer's disease. With all members of this class, continuous treatment is important for sustained effectiveness. If treatment is discontinued, the original level of effect may not be regained on resumption. Moreover, if the discontinuation lasts more than 3 days, treatment should be reinitiated at the lowest dose to reduce the risk of adverse effects. This is important to keep in mind — especially during the "donut hole" period of the Medicare Part D coverage, when the beneficiary is fully responsible for costs — when developing programs to promote adherence.

Memantine. Long used in Europe to treat Alzheimer's disease, memantine is the first glutamate pathway modifier approved for use in the United States, for patients with moderate to severe Alzheimer's disease.

Memantine is an antagonist of the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor, which controls the flow of calcium into nerve cells. Under

TABLE 3 Dosing of antideementia agents

Drug	Initial daily dosage	Titration	Final daily dosage	Common side effects
Cholinesterase inhibitors — mild to moderate disease				
Donepezil (Aricept)	5 mg, once daily, for 4–6 weeks (with or without food)	Increase to 10 mg, once daily, after 4–6 weeks	10 mg, once daily	Nausea, diarrhea, insomnia, vomiting
Galantamine (Reminyl)	4 mg, twice daily, for 4 weeks (with food)	Increase by 4 mg per dose every 4 weeks	8–12 mg, twice daily	Nausea, vomiting, loss of appetite, weight loss
Rivastigmine (Exelon)	1.5 mg, twice daily, (with food)	Increase by 1.5 mg per dose every 2 weeks	3–6 mg, twice daily	Nausea, vomiting, loss of appetite, weight loss
Tacrine (Cognex)	10 mg, 4 times daily, for 4 weeks (between meals if possible; with meals if mild GI disturbance occurs)	Increase by 10 mg per dose every 4 weeks	20–40 mg, 4 times daily	Elevated amino-transferase levels, nausea, vomiting
Glutamate pathway modifiers — moderate to severe disease				
Memantine (Namenda)	5 mg, once daily, for 1 week (with or without food)	Increase daily dose by 5 mg every week (i.e., to 5 mg, twice daily; then 5 mg and 10 mg given as separate doses; and finally, 10 mg, twice daily)	10 mg, twice daily	Dizziness, headache

GI=gastrointestinal.

SOURCE: MANUFACTURERS' PACKAGE INSERTS

the pathophysiologic conditions of advanced Alzheimer's, an overabundance of glutamate is believed to overexcite the NMDA receptors and lead to excessive calcium influx into neurons, resulting in their dysfunction and eventual death. Blocking the NMDA receptor thus attenuates the detrimental effects of a glutamate surfeit. (At other times, a glutamate *deficit* can occur in Alzheimer's patients; investigational products — such as Cortex Pharmaceutical's CX717, which enhances activity of the AMPA glutamate receptor subtype — are in early stages of development.) Memantine does not interfere with glutamate's action in the normal pathophysiologic memory process.

Ergoloid mesylates. Hydergine, a combination of an equiproportional mixture of three dihydro-derivatives (dihydroergocornine, dihydroergocristine, dihydroergocryptine), is an older agent used infrequently prior to approval of cholinesterase inhibitors. The mechanism of action is unclear; this agent has been associated with some alpha-blocking activity, however. It remains controversial whether the drug improves cerebral blood flow. The adverse effects of bradycardia, ergotism (nausea, vomiting, vasospastic ischemia), and transient gastrointestinal upset may limit this agent's use. The data behind the use of ergoloid mesylates differ greatly on the beneficial

or lack of beneficial effects of this drug for Alzheimer's disease. Due to the lack of an FDA indication for Alzheimer's disease treatment, and because FDA-approved agents with greater efficacy are available, Hydergine is used rarely.

Combination therapy. Combination therapy involving two or more cholinesterase inhibitors has not been studied. A cholinesterase inhibitor commonly is used in conjunction with memantine, however. In patients with moderate to severe Alzheimer's disease who already were taking donepezil, the addition of memantine has been shown to improve measures of cognition, ADL, behavior, and clinical global status, compared with placebo (Tariot 2004).

Physicians sometimes use high-dose vitamin E to supplement the prescription drugs discussed above. Medicare Part D does not provide for coverage of OTC products such as vitamin E and NSAIDs, despite some evidence that these agents may be beneficial in the treatment or prevention of Alzheimer's disease (Sano 1997, in t' Veld 2001).

Using high-dose vitamin E is controversial and should be reserved until larger, randomized, controlled clinical trials evaluate its efficacy and safety. A recent meta-analysis has reported that high-dose vitamin E (>400

TABLE 4 Monthly costs of informal and formal care of Alzheimer's patients*

Stage	Community setting, any			Assisted-living facility			Nursing home		
	Informal	Formal	Total	Informal	Formal	Total	Informal	Formal	Total
Mild	\$ 647	\$ 511	\$ 1158	\$77	\$ 2612	\$2689	\$35	\$ 3486	\$3521
Moderate	1120	755	1874	67	2431	2497	42	3497	3539
Severe	1129	1138	2266	88	2768	2856	34	3557	3591
All stages	866	683	1549	78	2609	2687	57	3073	3130

*Mean monthly costs in 1996 dollars. Some figures do not add to "total" due to rounding.
SOURCE: LEON 1998

IU/day) might increase all-cause mortality (Miller 2005).

Additionally, the Alzheimer's Association has lamented the omission of benzodiazepines from Medicare Part D coverage, noting that these agents are prescribed commonly for insomnia and anxiety in patients with Alzheimer's disease. Concurrent treatment with anti-psychotics or antidepressants, or both, may be appropriate for many Alzheimer's disease patients. These drugs are included in Medicare Part D, and for quality assurance purposes it will be important to ascertain that patients receiving antideementia agents also are receiving antipsychotics or antidepressants as is medically necessary.

Pharmacoeconomic considerations

A decade ago, annual direct and indirect national costs for care of patients with Alzheimer's disease were estimated at \$100 billion, with lifetime annual costs of caring for an individual patient estimated at \$174,000 (Ernst 1994). Most people with Alzheimer's are cared for at home. U.S. businesses spend \$25 billion annually in direct costs for Alzheimer's, and caregivers who are in the workforce cost U.S. businesses another \$36 billion annually in indirect costs, owing to absenteeism and lost productivity (Koppel 2002). The cost per patient varies with disease severity and the setting in which care is provided (Table 4).

In the study that generated the data for Table 4, just a 1-month delay in the institutionalization of a person with moderate or severe Alzheimer's was estimated to save \$1,863 per month in formal services (Leon 1998). A 1-month delay in institutionalization is a low estimate for treatment with currently available antideementia agents, and the projected savings would pay for many months of treatment with these agents.

It was calculated further that enabling a patient to stay in an assisted-living facility instead of a nursing home could yield average annual savings of \$9,312 per patient — up to \$5 billion nationwide. In reviewing donepezil, galantamine, and rivastigmine (tacrine was excluded because of hepatotoxicity), the Veterans Health

Administration concluded that the cost of these agents could be neutralized by reducing the cost of home care and delaying nursing home placement (VA 2004).

Because long-term nursing home care is financed chiefly through Medicaid, states are extremely concerned that underutilization of antideementia medications would result in the premature admission of Alzheimer's patients to nursing homes, with the states paying for such care. Policymakers therefore need to ensure that Medicare Part D formularies are constructed from a broad perspective, instead of focusing on the short-term financial benefits for a given pharmaceutical silo. Indeed, use of antideementia agents can be expected to increase as a result of the MMA, as Part D will reduce the economic burden for patients contemplating drug therapy for Alzheimer's disease, thereby lowering the threshold at which patients' costs exceed their benefits. As a consequence, the treatment span will be extended at both ends, with drug therapy being instituted earlier and continued longer.

Formulary design

The MMA stipulates that a formulary "must include drugs within each therapeutic category and class of covered part D drugs, although not necessarily all drugs within such categories and classes." In its guidance for the MMA, CMS "encourage[s] plans to submit formularies similar to those in widespread use today," and states "A formulary must include at least two drugs in each approved category and class (unless only one drug is available for a particular category or class)."

The guidance notes that CMS regards this requirement as a floor rather than as an absolute standard. The guidance further delineates that CMS will check whether a formulary provides appropriate access to drugs addressed in widely accepted national treatment guidelines for dementia.

By these criteria, any Part D formulary constructed in accordance with the USP Model Guidelines must contain memantine. In addition to being the only member of its class and the only antideementia agent indicated for treat-

ing moderate to severe Alzheimer's disease, memantine belongs to many formularies in use today.

Likewise, any Part D formulary must contain at least two cholinesterase inhibitors. If a plan elects to have only two cholinesterase inhibitors on its formulary, one of them should *not* be tacrine — because of its risk profile, the need for frequent dosing, and the lack of current use; serious consideration should be given to medications such as donepezil for the opposite reasons. Donepezil — the market leader — has the longest history of use among the remaining three agents, has been widely studied, and is found on formularies nationwide — partly due to its safety profile and ease of once-daily dosing. Either rivastigmine or galantamine should be added, if not both, because patients who fail to respond to one cholinesterase inhibitor may respond to another. Additionally, an appropriate transition plan needs to be developed, so that patients moving from a nonformulary medication do not suffer adverse effects from discontinuing one medication and starting another.

Conclusion

Beyond medication efficacy and safety, P&T committees must carefully consider quality assurance programs in the areas of transitioning, adherence, and treatment of comorbid conditions commonly associated with Alzheimer's disease. CMS is developing measures similar to those used by the National Committee for Quality Assurance in its Health Plan Employer Data and Information Set, to assure appropriate utilization of this category of medications. During selection of antedementia agents for a Part D formulary, P&T committees must look beyond the limited silos of prescription drug plans or Medicare Advantage prescription drug plans, basing their decisions on medical necessity. Nursing home placement, caregiver burden, and slowing of dementia's progression, while not directly affecting the Part D plans financially, should be remembered when P&T committees make decisions on this category of medications. The effects of these agents may be small, but they are highly meaningful to Alzheimer's patients and their caregivers.

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Tumor Necrosis Factor Inhibitors: Following Best Practice

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Clinical evidence supports the statement that tumor necrosis factor (TNF) inhibitors have revolutionized the nature of treatment for patients with rheumatoid arthritis (RA), juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, and Crohn's disease. These biologic agents can reduce signs and symptoms of inflammation in the joints, skin, and gut; lower serum markers of systemic inflammation; improve patient function and quality of life; and halt progressive joint damage. Their efficacy is proof of the central role of TNF in the pathogenesis of these chronic, inflammatory, autoimmune diseases.

Differences between TNF inhibitors

Variations exist among TNF inhibitors relative to duration and patient-years of experience in the marketplace, structures, mechanisms of action, pharmacokinetics, and efficacy and safety profiles (Table 1, page 18). The soluble TNF receptor etanercept (Enbrel), for example, binds soluble TNF- α and lymphotoxin (TNF- β), whereas anti-TNF monoclonal antibodies infliximab (Remicade) and adalimumab (Humira) bind soluble and membrane-bound TNF- α but not lymphotoxin. The soluble TNF receptor does not lyse cells; anti-TNF monoclonal antibodies do. The reported risks of developing tuberculosis (TB) vary and may be influenced by facilitated vs. nonfacilitated reporting, studies of European vs. North American populations, and presence or absence of prior TB screening tests. Neutralizing antibodies against etanercept do not develop (Amgen 2004), whereas neutralizing antibodies against infliximab and adalimumab occur in a minority of patients and have been associated with reduced efficacy and increased adverse events (Baert 2003, CDER 2003).

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Comparing TNF inhibitors

Pharmacy and therapeutics committees should consider several methodological differences in clinical trials when reviewing literature to assess potential outcomes of patients to be treated with TNF inhibitors. Unfortunately, available clinical data comparing TNF inhibitors are not straightforward. Several issues to consider include:

- No head-to-head trials directly compare safety or efficacy of the different TNF inhibitors.
- Few placebo-controlled trials utilize TNF inhibitors in RA; most use an active comparator arm.
- Clinical trials of biologic therapies in RA have used different inclusion criteria. Aspects of trial design to consider when comparing efficacy include disease activity of the treated population and underlying degree of functional disability; duration of illness when the patient was treated initially; previous response to methotrexate (no previous exposure, sub-optimal response, or failure); and previous response to other disease-modifying antirheumatic drugs (DMARDs), as measures of refractory disease.
- Combination therapy with methotrexate and a TNF inhibitor may be more effective than monotherapy with the TNF inhibitor. Therefore, efficacy results of biologic therapies in clinical trials in which the biologic agent is used as monotherapy should not be combined, nor should they be compared with results when biologics are used in combination therapy with methotrexate.
- Neutralizing anti-TNF inhibitor antibodies have been associated with reduced clinical efficacy or increased drug reactions. Immunogenicity of TNF inhibitors also becomes important in understanding the possible roles of methotrexate in combination therapy: In some cases, it may enhance TNF inhibitor therapy through complementary mechanisms of action; in other cases, it may be required to achieve and or sustain therapeutic effect because it prevents development of neutralizing antibodies.
- Comparative analyses will be limited to outcomes reported consistently in randomized clinical trials in RA. These outcomes include the American College of Rheumatology (ACR) 20, 50, and 70 scores as composite measures of efficacy in relieving signs and symptoms of RA, the total Sharp score as a

TABLE 1 Differences between tumor necrosis factor (TNF) inhibitors

	Etanercept	Infliximab	Adalimumab
First approval	October 1998	November 1999	December 2002
Indications ¹⁻³	Rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis	Rheumatoid arthritis, ankylosing spondylitis, Crohn's disease	Rheumatoid arthritis
Estimated patient-years of exposure through 2003 ^{4,5}	>290,000	>500,000	>16,000
Structure ¹⁻³	Soluble p75 TNF receptor fusion protein	Anti-TNF monoclonal antibody	Anti-TNF monoclonal antibody
Administration ¹⁻³	Self-injection, subcutaneous	Health care facility, intravenous	Self-injection, subcutaneous
Serum half-life ¹⁻³	102+30 hours	8.0-9.5 days	10-20 days
Dose ¹⁻³	50 mg every week (q wk) or 25 mg twice a week (bi wk) — except in psoriasis, which is 50 mg bi wk x 12 wks then 50 mg q wk	3 mg/kg loading doses at weeks 0, 2, 6; then 3-10 mg/kg q 4-8 weeks	40 mg every other wk (qo wk) to q wk
Binds ¹⁻³	Soluble TNF- α and TNF- β and inhibits their binding to cell surface p55 and p75 TNF receptors; no C1 binding	Soluble and transmembrane TNF- α and inhibits binding of TNF- α to cell surface p55 and p75 TNF receptors; C1 binding	Soluble and transmembrane TNF- α and inhibits binding of TNF- α to cell surface p55 and p75 TNF receptors; C1 binding
Fc-mediated cell lysis ¹⁻³	No	Yes	Yes
Effectiveness in granulomatous diseases ^{2,6-8}	No (Crohn's, Wegener's)	Yes (Crohn's)	Yes (Crohn's) in initial studies
Estimated risk of tuberculosis (TB), n/100,000 patients ⁹⁻¹³	10-12	36-53	150-1300
Proportion of patients with neutralizing anti-TNF inhibitor antibodies ¹⁻³	0	10%	1% with methotrexate, 12% without methotrexate
Boxed warnings ¹⁻³	None	Risk of infection, TB; need TB screening	Risk of infection, TB; need TB screening

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measure of joint damage, and the Health Assessment Questionnaire (HAQ) as a measure of patient function.

- Ability to reduce or discontinue concomitant medications, such as methotrexate or corticosteroids, and effect on employment outcomes may be informative measures of efficacy.
- The need for dose escalation of the biologic agent to achieve or maintain a clinical response in real-world settings is appropriate to evaluate as a surrogate for reduced efficacy in these situations.
- Efficacy should include sustainability of response and should take long-term experience into account.
- Outcomes should be compared at the same time point after treatment initiation (3, 6, and 12 months are most commonly reported in randomized clinical trials in RA).
- Differences in statistical approach merit consideration when comparing trial results. Some statistical approaches are more conservative than others, with methods ranging from intent-to-treat analyses to last-observation-carried-forward analyses to non-responder imputation.

Pharmacy and therapeutics committees need also to assess relative safety of therapies when making formulary decisions. Issues to consider during evaluation of relative safety of TNF inhibitors in RA include the following:

- Evaluation of safety should assess numbers of patients exposed to the agents, duration and patient-years of exposure, and methods used to ascertain adverse events. Comparing the safety data of biologics with limited exposure against agents with greater exposure may produce bias in favor of the former, because in these agents there is less opportunity for uncommon events to occur.
- Patient characteristics may influence safety profile. Evaluation of safety of TNF inhibitors should include safety in special populations (e.g., pregnant women, children, elderly patients, patients with comorbidities). Interactions of these drugs with commonly used medications in RA patients, such as methotrexate and digoxin, should be considered.
- Safety and tolerability evaluations should include common side effects (SEs) with TNF inhibitors (e.g., infusion- and injection-site reactions); and uncommon yet serious SEs (e.g., liver disease, TB and opportunistic infections, malignancies, lymphomas, demyelinating diseases, systemic lupus erythematosus).
- Analyses of rates of adverse events in voluntary databases should allow for differences in sources of reports; agents for which reporting of adverse events is facilitated may have higher rates of adverse events reported than agents for which this does not occur.

Multiple cost-effectiveness models of TNF inhibitors in RA have been published. Considerations for comparative evaluations of the results of these models include:

- Quality of life and disease activity.
- Pattern of serial drug use in the real world and drug costs (including costs related to dose escalation, administration, and required laboratory testing).
- Costs of other RA medications required to control disease activity and costs of RA-related physician and hospital services as part of total costs of RA.
- Data for the model taken from the same time point and, preferably, at 1 year of therapy minimum.

Treatment guidelines

Guidelines from professional and lay organizations outline the role of biologic therapies in the treatment of patients with RA, ankylosing spondylitis, psoriatic arthritis, psoriasis, and Crohn's disease, and suggest populations for whom these therapies would be appropriate.

Rheumatoid arthritis. The Centers for Medicare and Medicaid Services (CMS) will use RA as one disease for which it analyzes formularies to determine whether appropriate access is afforded to drugs addressed in widely accepted national treatment guidelines. An international consensus statement indicates that after an adequate trial of another effective DMARD, biologic therapies generally are appropriate for patients with active RA (Furst 2004). ACR treatment guidelines state that TNF inhibitors are the most clinically effective anticytokine therapy studied to date and "represent a major advance in the treatment of RA" (ACR 2002). These guidelines indicate that initiation of a DMARD should not be delayed beyond 3 months of disease in any patient with symptoms while on nonsteroidal anti-inflammatory (NSAID) agents only. Patients with ongoing active RA, despite adequate doses of methotrexate (or patients with methotrexate intolerance), are appropriate for TNF inhibitors alone or in combination with nonbiologic DMARDs. It is important to note that the ACR guideline was published in early 2002 and has not been updated to reflect new clinical trial information or labeling changes that indicate efficacy of TNF inhibitors as first-line treatment for active moderate-to-severe RA (Amgen 2004).

Ankylosing spondylitis. Guidelines (Braun 2003, Spondylitis Association 2004, Maksymowich 2002) suggest that ankylosing spondylitis patients are appropriate candidates for TNF inhibitor therapy if they have: (1) been diagnosed by modified New York criteria (Van der Linden 2002); (2) moderate to severe ankylosing spondylitis; (3) the presence of active disease for at least 4 weeks; (4) a Bath Ankylosing Spondylitis Disease Activity Index score greater than 4 cm (scale 0–10 cm) and physician global assessment of 2 or greater on a Likert scale (0=none, 1=mild, 2=moderate, 3=severe, 4=very severe);

and (5) failure by lack of response or intolerability to at least two NSAIDs during a single 3-month period for all three clinical presentations: axial, peripheral arthritis, and enthesitis. Patients with peripheral arthritis must have failed by lack of response or intolerability to one DMARD for peripheral arthritis.

Psoriatic arthritis. Because of limited proof of the value of conventional DMARDS as a treatment option for patients with psoriatic arthritis (Furst 2004), patients with active psoriatic arthritis (3 or more tender and 3 or more swollen joints) may be considered appropriate candidates for biologic therapy (International Consensus Conference 2004, AAD 2003, NPF 2003). Though affected patients might have limited skin involvement (i.e., visible disease), aggressive systemic therapy is necessary.

Psoriasis. Guidelines indicate that psoriasis patients who are appropriate for treatment with biologic therapy are the same patients who are candidates for systemic therapy (International Consensus Congress 2004, AAD 2003, NPF 2003). As outlined in these guidelines, psoriasis patients who are candidates for systemic therapies include those who meet any one of these criteria: (1) patients with moderate to severe plaque psoriasis who are candidates for systemic therapy; (2) patients with psoriasis of the palms, soles, head and neck, or genitalia, or with more than 5 percent body surface area involvement and who may be considered to have moderate to severe disease; (3) patients for whom topical therapy is ineffective or impractical; (4) patients who have failed on, or are intolerant of, current nonbiologic systemic therapies; (5) patients for whom current nonbiologic systemic therapies or phototherapy are impractical; (6) patients with recalcitrant psoriasis; (7) patients with severe impairment of quality of life and/or physical or psychosocial disability; (8) patients who are physically incapacitated (unable to use topical or ultraviolet therapy). In addition, biologic therapy may be appropriate for certain other psoriasis patients, on a case-by-case basis, based on the need for practical monotherapy or a long-term therapeutic option, particular safety concerns, or requirements for biologics in transition from one systemic therapy to another.

Crohn's disease. General principles to consider in determining optimal treatment include the site (e.g., ileal, ileocolic, colonic); pattern (e.g., inflammatory, stricturing, fistulating); and activity of the disease. Infliximab (5 mg/kg) should be reserved for patients with moderate-to-severe Crohn's disease who are refractory to or intolerant of treatment with steroids, mesalazine, azathioprine/mercaptopurine, and methotrexate and where surgery is considered inappropriate (Carter 2004).

New treatment paradigm

Rheumatoid arthritis. Rheumatoid arthritis is a chronic inflammatory arthritis characterized by variable disease onset and clinical course, with the potential for structural

joint destruction leading to permanent disability (Hochberg 1993). It is estimated to affect between 0.5 percent and 1.0 percent of adults; it increases in prevalence with age and affects more women than men. RA is most prevalent in those who are age 65 or older (Mitchell 1985, Robinson 1986). The disease is commonly diagnosed between ages 30 and 50, but up to 33 percent of subjects may be diagnosed after age 60 (Terkeltaub 1983, Papadopoulos 2003).

RA is chronic and progressive in most patients. As described in a recent pharmacoeconomic review by Kvien (2004), most patients require continuous treatment to retard or stop progression and to control disease flares. Surgery, such as total hip or knee replacement, may be required. In addition to these direct costs, work disability leads to reduced productivity and early retirement, and, as a result, substantial indirect costs. Patients with RA have a mean reduction in life expectancy of between 5 and 10 years. Disease severity, activity, and disability are strongly linked to premature mortality in patients with RA.

Prior to the introduction of biologic therapies for RA, which include both TNF inhibitors and interleukin-1 inhibitors (anakinra), perhaps the most effective nonbiologic DMARD therapy was methotrexate. The introduction of TNF inhibitors brought greater control of disease activity than had been seen with conventional DMARDS, and expectations of treatment outcomes rose. Now, disease remission, including improvement in patient function and halting of progressive joint damage, is the desired outcome of therapy in RA (Pincus 2004), with acceptable risk of SEs and patient convenience.

Treatment paradigms in RA have evolved to reflect physician appreciation that signs and symptoms of inflammation and joint damage can and must be controlled, and control of signs and symptoms of inflammation by a DMARD does not imply control of joint damage. Rheumatologists now recognize that treatment needs to be most aggressive in early RA, because 70 percent of patients who develop joint erosions will do so within the first few years of disease (van der Heijde 2000). In addition, early treatment provides improvement in patient-reported outcomes (Baumgartner 2004). Rheumatologists also have come to realize that combination therapy with a traditional DMARD plus a TNF inhibitor may provide greater efficacy than either monotherapy in certain patients (Klareskog 2004).

For patients with moderate to severe RA, many rheumatologists now start methotrexate or another DMARD at the first patient visit, quickly escalate the dose of the DMARD to optimal levels (which may be limited by patient tolerance), then start a biologic agent if control of signs or symptoms of joint inflammation remain suboptimal or if progressive joint damage is found. Payers may be less aware of this shift in the treatment model, from slow step-up therapy with multiple sequential

DMARDs to early aggressive combination therapy with a DMARD plus TNF inhibitor.

Part D formularies

As a specific example of the usefulness of TNF inhibitors in treating chronic, inflammatory, autoimmune diseases in Medicaid patients, this discussion will focus on RA and treatment with one of the most effective medications for this disease — etanercept.

Efficacy and safety. Etanercept controls signs and symptoms of inflammation (as identified by ACR scores and Disease Activity Score [DAS] responses), can induce low disease activity and remission by DAS criteria, can improve patient function and employment outcomes, and can halt progressive joint damage (Table 2). Etanercept is the only TNF inhibitor with a label for major clinical response in RA, which means patients can maintain an ACR70 response for at least 6 months. With etanercept therapy, responses are prompt and predictable — with the majority of patients achieving an ACR20 response within 8 weeks.* This soluble TNF receptor is effective in both early RA and DMARD-refractory RA.* Etanercept in combination with methotrexate has superior efficacy to etanercept or methotrexate monotherapy, as defined by its effect in achieving ACR20, 50, and 70 responses, improving patient function as measured by HAQ responses, and halting progression of joint damage (Klareskog 2004). Nonetheless, etanercept can be used as monotherapy in those patients who cannot tolerate methotrexate or in whom methotrexate is contraindicated.* Long-term efficacy is predictable and sustainable in the treatment of moderate to severe RA (Moreland 2001). Patients treated with etanercept have limited dose increases (Abarca 2004). In addition, etanercept has been used in more RA patients than any other biologic agent. Long-term efficacy of etanercept has been demonstrated for up to 7 years in clinical trial experience with etanercept at 50 mg per week (Amgen 2004). Patients who fail to respond to infliximab have a clinical response to etanercept (Buch 2005, van Vollenhoven 2003).

Infusion reactions are the most frequent SE of etanercept and are usually mild. Uncommon but more severe adverse events include infections such as pneumonia, TB, and opportunistic infections. Other potential serious SEs include malignancy, lymphoma, demyelinating diseases, and systemic lupus erythematosus. Etanercept does not interact with medications that are com-

monly used in RA patients, such as digoxin and methotrexate (Amgen 2004). Etanercept is safe and well-tolerated in RA patients ages 65 and older and in patients with comorbid diseases (Baumgartner 2004). Geriatric patients have a likelihood of gaining the benefits of etanercept that equals that of younger patients (Fleischmann 2003).

In support of the favorable benefit-to-risk ratio of etanercept in RA, etanercept is available on nearly all managed care formularies and in Medicaid systems. Etanercept is the biologic immune suppressant most commonly used in the treatment of RA, ankylosing spondylitis, psoriatic arthritis, and psoriasis.

Patient preference, access, and convenience. Patient preferences for etanercept, gold, methotrexate, and leflunomide were determined by asking patients to make trade-offs between specific treatment characteristics. Based on its safety and efficacy characteristics, etanercept was found to be the preferred therapy for RA in 95 percent of 120 elderly (mean age, 70 years) RA patients (Fraenkel 2004).

Self-administration of etanercept allows its use in patients in rural areas and in underserved areas where patients do not have ready access to infusion centers. Patients can select the timing and method of etanercept administration — once or twice weekly using lyophilized powder, or with a prefilled injectable syringe. Amgen's 1-888-4ENBREL access program provides help to physi-

TABLE 2 Efficacy of etanercept in the treatment of rheumatoid arthritis (RA)

Improves signs and symptoms of inflammation
Pain
Tender and swollen joints
ACR20, 50, and 70 responses
DAS28 (EULAR) moderate or good responses
DAS28 remission
Major clinical response (ACR70 response for >6 months)
Improves serum measures of inflammation (erythrocyte sedimentation rate, C-reactive protein)
Improves patient function
Health Assessment Questionnaire
Short-Form 36 physical and mental function domains
Patient global assessment
Employment
Halts progressive joint damage (total Sharp score)
Joint-space narrowing
Bone erosions

ACR=American College of Rheumatology; DAS=Disease Activity Score; EULAR=European League Against Rheumatism.

SOURCES: AMGEN 2004; BATHON 2000; BAUMGARTNER 2004; GENOVESE 2002; KLARESKOG 2004; MORELAND 1999, 2001; WEINBLATT 1999; YELIN 2003.

* See references, Table 2.

cians and patients to determine eligibility for etanercept therapy and access to Amgen's patient-support program. Participation in the patient-support program is associated with greater patient persistence on medication.

Cost effectiveness.[†] Treatment of RA patients with etanercept is cost-effective vs. monotherapy (Brennan 2004) or combination therapy (Kobelt 2005), compared with DMARDs. An analysis by Brennan (2004) examined the cost-effectiveness of etanercept monotherapy in accordance with the British Society of Rheumatology guidelines and quantified the cost per Quality Adjusted Life Year (QALY) gained through use of etanercept compared with current care in the United Kingdom. This was a lifetime analysis; costs in the model included those for medication and monitoring, as well as other direct health care costs. The calculated incremental cost-effectiveness ratio (ICER) for etanercept monotherapy was \$29,433. The inclusion of employment productivity savings improved the cost per QALY to \$21,500. The conclusion was that etanercept monotherapy was cost-effective, and the National Institute for Clinical Excellence used the data as evidence to accept etanercept in the United Kingdom.

Combination therapy with etanercept and methotrexate is cost-effective versus methotrexate alone, based on effectiveness data from a 2-year trial in 682 patients with active RA (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) (Brennan 2004). A Markov model was constructed with five states according to functional status (as defined by the HAQ), subdivided into high and low disease activity. Disease activity had a highly significant effect on utilities, independent of HAQ. For resource consumption, only HAQ was a significant predictor, with the exception of sick leave. Compared with methotrexate alone, etanercept plus methotrexate over 2 years increased total costs by \$14,221 and led to a QALY gain of 0.38. When treatment is continued for 10 years, incremental costs are \$42,148 for a QALY gain of 0.91.

A model by Chiou (2004) showed etanercept to be more cost-effective than treatment with infliximab and adalimumab. This included medication and direct resource costs (physician visits, laboratory costs, clinical care, and hospitalization for adverse events). Etanercept was cost-effective based on an ICER of \$13,985, with improvement in its value as combination therapy with methotrexate, with an ICER of \$8,279. In the same study, adalimumab combination therapy with methotrexate costs per QALY were \$11,397, whereas infliximab plus methotrexate therapy costs per QALY were \$119,578. Reasons for the superior cost-effectiveness of etanercept include higher efficacy in clinical trials, dose escalation with both monoclonal antibodies, and administration costs for infliximab.

Part D demonstration project. Etanercept is approved

[†] All figures in this section are in 2004 U.S. dollars.

for the Medicare Part D Demonstration Project of the Medicare Prescription Drug, Improvement and Modernization Act of 2003. CMS chose drugs for the demonstration project based on criteria that included: (1) at least of equal efficacy to the covered Part B drug for which it is a replacement; and (2) an advantage in terms of access and/or convenience for patients compared to the currently covered drug or biologic (CMS 2004). After the beginning of the demonstration, CMS expanded covered indications for etanercept to include psoriatic arthritis, psoriasis, and ankylosing spondylitis.

CMS expects that best practice Part D formularies will contain "a majority" of drugs within the immune suppressant class, which includes TNF inhibitors. In addition, as part of its analysis of the adequacy of proposed Medicare Part D formularies, CMS will review formularies for at least one drug in each of the Formulary Key Drug Types identified by United States Pharmacopeia. Etanercept is a widely used immune suppressant that fulfills the TNF inhibitors category. CMS will analyze formularies to determine whether appropriate access is afforded to drugs addressed in widely accepted national treatment guidelines for RA. As discussed above, etanercept provides guideline-recommended biologic coverage for RA, and it is the only self-injectable TNF inhibitor that is approved by the U.S. Food and Drug Administration that also provides guideline-recommended treatment for ankylosing spondylitis, psoriasis, and psoriatic arthritis.

CMS has stated that Medicare Part D formularies should not discourage enrollment of beneficiaries with certain diseases by failing to provide access to treatments recommended by professional guidelines; one technique that could limit access includes use of restrictive, tiered cost-sharing structures. In addition, CMS review will review formularies for their potential to discourage enrollment of certain beneficiaries by placing drugs in non-preferred tiers in the absence of commonly used therapeutically similar drugs in more preferred positions. To gain CMS approval, formularies will need to provide access to medications that fulfill all the requirements outlined in the CMS guidance.

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Bisphosphonates: Providing Strength To a Significant Class

BRUCE ETTINGER, MD

The bisphosphonates constitute one of the most crowded therapeutic classes of drugs in the United States. Led by alendronate (Fosamax), they ranked 11th in use among therapeutic classes in 2004, generating \$3.6 billion in wholesale sales (Figure). Although utilization continues to grow at double-digit rates, the rate of growth is slowing. Sales increased 30 percent between 2001 and 2002; growth rates declined to 22 percent and 15 percent in the succeeding years.

Most bisphosphonate use is for prevention or treatment of postmenopausal osteoporosis, but these agents also are used to treat Paget's disease and to counteract bone-related effects of malignancies (Table). By the nature of these indications, bisphosphonates are most likely to be prescribed for the Medicare population. Accordingly, the Centers for Medicare and Medicaid Services (CMS) designated bisphosphonates as a key drug type in the pharmacologic class of parathyroid/metabolic bone disease agents. This article discusses selection of bisphosphonates for formularies under Part D of the Medicare Prescription Drug, Improvement and Modernization Act of 2003 (MMA).

Treatment and prevention of osteoporosis

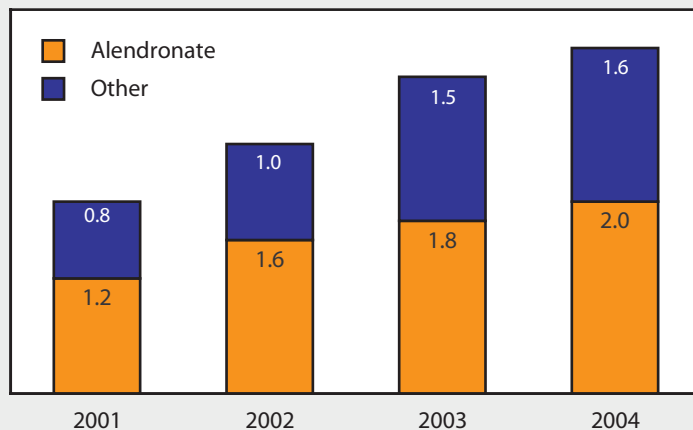
The National Osteoporosis Foundation (NOF) estimates that in the United States, 8 million women and 2 mil-

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lion men over age 50 have osteoporosis. Osteoporosis is responsible for 1.5 million fractures annually, the most fearsome being hip fractures — at a rate of 300,000 per year.

The estimated prevalence of osteoporosis is based on a quantitative definition of the condition in which a pa-

FIGURE Bisphosphonate sales (wholesale)
\$ Billions



SOURCE: IMS 2005

tient's bone mineral density (BMD) is compared with the mean BMD of healthy young adults of the same sex. The results are expressed as T-scores, which express the patient's BMD in terms of standard deviations (SD) from the healthy-young-adult mean. Normal BMD is less than 1 SD below that mean (i.e., a T-score above -1), whereas a patient whose T-score is below -2.5 is said to have osteoporosis. A patient whose T-score is below -2.5 and who has had one or more osteoporotic fractures is said to have severe or established osteoporosis.

People whose T-scores are between -1 and -2.5 are said to have *osteopenia*, or low bone mass. NOF estimates that 34 million Americans are in this group. Thus, some 44 million Americans already have osteoporosis or may be at risk of developing it on the basis of their BMD.

Nevertheless, BMD alone is insufficient for determining risk of fracture and need for drug therapy. For example, in a community-based study enrolling women ages 65 and above, 17 percent of the 8,065 participants with adequate BMD measurements were found to have osteoporosis on the basis of a T-score that was less than

TABLE Indications and year of FDA approval for currently available bisphosphonates

	Alendronate (Fosamax)	Etidronate (Didronel)	Pamidronate (Aredia, generics)	Risedronate (Actonel)	Tiludronate (Skelid)	Zoledronic acid (Zometa)
Nonmalignant bone disorders						
Osteoporosis treatment, postmenopausal women	1995			2000		
Osteoporosis prevention, postmenopausal women	1997			2000		
Osteoporosis treatment, men	2000					
Glucocorticoid-induced osteoporosis	1999 (treatment only)			2000 (prevention and treatment)		
Paget's disease	1995	1977	1994	1998	1997	
Heterotopic ossification		1977				
Cancer-related disorders						
Osteolytic bone metastases			1996 (breast cancer)			2002 (solid tumors)
Osteolytic lesions of multiple myeloma			1995			2002
Hypercalcemia of malignancy			1991			2001

SOURCES: MANUFACTURERS' PACKAGE INSERTS

or equal to -2.5 (Wainwright 2005). These subjects were followed for up to 5 years. Among the 234 women who sustained a hip fracture during follow-up, 54 percent were *not* osteoporotic at the beginning of the period. The non-osteoporotic BMD patients with hip fracture could be distinguished by other characteristics, however, such as advancing age, lack of exercise during the previous year, reduced visual-contrast sensitivity, falls during the previous year, and vertebral fracture on spine X-ray. A more targeted approach for identifying candidates for drug therapy, therefore, would exploit fracture prediction models that use BMD in conjunction with clinical risk factors to estimate a patient's absolute 5- or 10-year risk of fracture (Black 2001, Ettinger 2005).

In healthy bone tissue, during the remodeling process, osteoblasts construct new bone at the same rate at which osteoclasts remove old bone. Osteoporosis develops when osteoclasts remove old bone faster than osteoblasts replace bone in the resorption spaces created by the osteoclasts. Under normal conditions, about 5 percent of bone is renewed each year; this process continuously replaces old bone with new and repairs microscopic damaged bone.

Bisphosphonates, the gold standard for treating osteoporosis, suppress the activity of osteoclasts, thereby reducing bone turnover. During the first 6 months or so of treatment, BMD increases by 2 to 3 percent as available resorption spaces are filled in and few new resorption cavities are formed. After that, BMD continues to increase, by perhaps 1 percent per year, owing to increased miner-

alization resulting from the growth of existing hydroxyapatite crystals on bone collagen matrix. Reducing bone turnover is a key factor in reducing fracture risk.

Enhancing bone mineralization also may contribute to improved bone strength. Animal models based on high-dose bisphosphonate exposure have suggested, however, that excessive suppression of bone turnover results in less-healthy bones due to accumulation of microscopic damage and brittleness from excessive mineralization. Despite these theoretical limitations, in clinical trials bisphosphonates show efficacy in reducing risk of fracture (Black 1996, Cummings 1998, Harris 1999, Reginster 2000).

Measuring BMD is inadequate as a tool for monitoring treatment effectiveness. First, fracture risk reduction is not closely related to increments in BMD. Second, the precision of the BMD measure is limited, with an error rate of 3 percent under optimal circumstances. The error rate also marginalizes BMD measurement as a tool for improving patients' adherence to therapy, as sometimes is advocated. A majority of patients fail to comply with any drug therapy for osteoporosis during the first months (McCombs 2004), before any increase in BMD becomes apparent. Improving adherence is better accomplished through support from health care personnel than from a BMD test result and can be much less costly.

HEDIS osteoporosis measure

The Medicare drug benefit is being created at a time when the National Committee for Quality Assurance

(NCQA) is focusing on appropriate use of bisphosphonates through adoption of a new measure in the Health Plan Employer Data and Information Set (HEDIS). This measure, "Osteoporosis Management in Women Who Had a Fracture," was reported voluntarily by Medicare plans in 2004 but will be a regularly reported measure in 2005 for all Medicare plans participating in HEDIS.

The new HEDIS measure estimates the percentage of women age 67 or older who suffered a fracture and then, within 6 months after the fracture, had a test of their BMD or received a prescription for a drug to prevent or treat osteoporosis. Among the 113 plans that submitted data from 2003, the mean rate at which qualifying women were so managed was 18 percent, evenly divided between BMD tests and prescriptions (NCQA 2004). For plans in the 90th percentile, the rate was 26.4 percent. As low as that may seem, it is still more than twice the national average found a few years ago (Andrade 2003).

For the present purpose, it is important to note that the new HEDIS measure focuses on high-risk patients (i.e., those who already have experienced a fracture) in the Medicare population (and only in the Medicare population). In this respect, it represents an important shift in attitudes toward osteoporosis among physicians.

A decade ago, emphasis was on screening women for low BMD at menopause to identify candidates for drug therapy intended to reduce their risk of a first fracture. Today, the recommendation of the U.S. Preventive Services Task Force is for BMD screening tests to be used routinely for women 65 and older, or at age 60 for women with clinical risk factors that put them at increased risk for osteoporotic fracture (USPSTF 2002). Drug therapy is now aimed at women who present a high risk of fracture. Among the patients at highest risk are those who already have suffered a fracture; hence the interest of the NCQA in assessing the management of this population.

Six-year results from the Early Postmenopausal Intervention Cohort (EPIC) study suggest unfavorable economics of bisphosphonate treatment in healthy early postmenopausal women. Among 585 women who received continuous daily treatment with placebo or alendronate 5 mg, the fracture rates were 11.5 percent and 8.9 percent, respectively, over 6 years (McClung 2004). For the alendronate group, the absolute risk reduction (ARR) of 2.6 percent over 6 years translates into an annual ARR of 0.4 percent. Thus, in this population of healthy early postmenopausal women, about 230 would have to receive alendronate 5 mg for 1 year at a cost of about \$160,000 to prevent one clinical fracture (weighted average cost, \$780 per fracture averted). Further, that fracture is likely to be a wrist fracture, not the more costly hip fracture.

In contrast, the logic of reserving bisphosphonate therapy for postmenopausal women at higher risk of osteoporotic fracture is borne out by different arms of the Fracture Intervention Trial (FIT). Both arms enrolled pa-

tients with low BMD (T-scores of -1.6 or lower); in one arm, the women had a history of vertebral fractures (Black 1996) and, in the other, they did not (Cummings 1998).

In the first study, after 3 years of follow-up, hip fractures were experienced by 2.2 percent and 1.1 percent of the placebo and alendronate groups, respectively, a relative risk reduction (RRR) of 51 percent. The 3-year rate of any clinical fracture was 18.2 percent and 13.6 percent in the placebo and alendronate groups, respectively, a RRR of 28 percent. In the second study, the rates of hip fracture and any clinical fracture in the placebo group were 1.1 percent and 14.1 percent, respectively — lower than the fracture incidences observed in the placebo group in the first study and comparable to the fracture incidences reported in the alendronate group in that study. The only subgroup of patients to experience a statistically significant reduction in clinical fracture risk were patients whose T-scores were lower than -2.5 . In this subgroup, clinical fractures were observed in 19.6 percent and 13.1 percent of the placebo and alendronate groups, respectively, a RRR of 46 percent after 4 years of follow-up.

These results support the concept of reserving bisphosphonate treatment for women who are at higher risk of osteoporotic fracture. For women at lower risk, preventive strategies should embrace adequate intake of calcium and vitamin D, weight-bearing exercise, and strength-and-balance training aimed at reducing risk of fall. Postmenopausal women who walked for 4 hours a week, in the absence of any other exercise, reduced their risk of hip fracture by 41 percent compared with women who walked less than 1 hour per week (Feskanich 2002). Medicare Part D plans that provide coverage for calcium and vitamin D because of their clinical significance must use non-Part D funds because, legislatively, over-the-counter medications are excluded from Part D coverage.

Bisphosphonates for Paget's disease

Paget's disease is a chronic disorder characterized by enlarged and deformed bones, owing to irregular rapid remodeling occurring in the later stages of the disease in response to excessive resorption in the early stages. Paget's disease rarely is diagnosed in people younger than 40, and its prevalence rises sharply with increasing age. Therefore, most people with Paget's disease are in the Medicare population or are approaching Medicare eligibility.

Extrapolating from a review of pelvic radiographs collected during the first National Health and Nutrition Examination Survey, researchers have estimated the overall prevalence of Paget's disease in the United States at 1 to 2 percent (Altman 2000). Between 2.5 million and 5 million Americans, therefore, may have Paget's disease. Yet, the disease is undiagnosed in a majority of these persons because it tends to be asymptomatic.

Localized bone aching at the site of Paget's is the most common symptom, but more severe presentation in-

cludes fracture, bone deformity, and nerve or spinal cord compression. Paget's disease cannot be cured, but usually it can be put into remission with drug treatment, which is quite effective in relieving pain and stopping disease progression. Disease severity and response to therapy commonly are assessed by measuring serum levels of alkaline phosphatase, a biomarker for disease activity.

Bisphosphonates are the treatment of choice, administered at higher doses than are used to treat osteoporosis, but usually only for 2 to 6 months. In most cases, a single course of therapy is adequate. Note that pamidronate is available only through intravenous administration — 30 mg given via a 4-hour infusion on 3 consecutive days, for a total dose of 90 mg. Intravenous medications are not specifically excluded under Part D, but many plans will maintain coverage under Part B where appropriate.

Bisphosphonates for cancer-related conditions

Pamidronate and zoledronic acid are administered intravenously to treat conditions associated with malignancies — hypercalcemia of malignancy and osteolytic lesions (Table, page 25). As with treatment for osteoporosis or Paget's disease, their target is the osteoclast, not a cancerous cell.

The efficacy of bisphosphonates in treating patients with bone metastases was established through use of a composite endpoint, a skeletal-related event (SRE). This measure of morbidity includes pathologic fractures, radiation to bone lesions, surgery to bone, and spinal cord compression. Both agents have been shown to reduce the time to first SRE, but zoledronic acid can be administered in a 15-minute infusion, whereas pamidronate necessitates an infusion of at least 2 hours for patients with hypercalcemia of malignancy or 4 hours for osteolytic bone lesions of multiple myeloma.

Formulary construction

The MMA stipulates that a formulary “must include drugs within each therapeutic category and class of covered part D drugs, although not necessarily all drugs within such categories and classes.” In its guidance, CMS “encourage[s] plans to submit formularies similar to those in widespread use today,” and states that “A formulary must include at least two drugs in each approved category and class (unless only one is available for a particular category or class).” CMS regards this requirement as a floor rather than as an absolute standard. Further, CMS will check whether a formulary provides appropriate access to drugs mentioned in widely accepted national treatment guidelines for osteoporosis. Where a key drug type is listed in the model guidelines, as bisphosphonates are so designated, it is CMS's expectation that at least one drug of the type will be included on a formulary.

It is reasonable for a formulary to include alendronate or risedronate, if not both, as these are the only bispho-

sphonates available with indications for the prevention and treatment of postmenopausal osteoporosis and glucocorticoid-induced osteoporosis. Both are included on formularies in widespread use, and both are covered under the Medicare Replacement Drug Demonstration for patients with Paget's disease or for home-bound patients with postmenopausal osteoporosis.

Alendronate is the long-established market leader, with the additional advantage of being the only bisphosphonate indicated for treatment of osteoporosis in men. Both alendronate and risedronate are supplied as once-daily or once-weekly tablets; alendronate also is available as a once-weekly oral solution for patients with swallowing difficulties. Weekly tablets account for the vast majority of bisphosphonate utilization because of lower gastrointestinal irritation and convenience of use.

When taking any formulation of either agent, the patient is instructed to take the drug on arising, with water only; to abstain from food or other beverages for at least 30 minutes; and to remain upright for at least 30 minutes and until after the first meal is eaten. Two considerations prompt these instructions. First, bisphosphonates are very poorly absorbed and are less well absorbed when taken with food. Second, bisphosphonates may cause esophageal irritation and ulceration, especially if the pill remains in contact with the esophagus for long periods.

In part due to these burdensome dosing restrictions, nearly half of osteoporosis patients discontinue treatment with the once-daily tablets after only 6 months. Because of their greater convenience and greater tolerability, the once-weekly formulations are much preferred. Even so, only 44 percent of postmenopausal women initiating osteoporosis treatment with a once-weekly bisphosphonate adhered to their therapy for 1 year (Cramer 2004). (Among women using a once-daily bisphosphonate, the 1-year adherence rate was 32 percent.)

Neither of the once-weekly formulations holds a clear advantage over the other. In a recent 1-year trial comparing alendronate 70 mg with risedronate 35 mg in women with postmenopausal osteoporosis (Rosen 2005), there was no statistically significant difference in the frequency of gastrointestinal adverse events (alendronate, 22.5 percent [116/515]; risedronate, 20.1 percent [106/527]).

Despite greater gains in BMD and greater reductions in markers of bone turnover seen in the alendronate group, neither was there any statistically significant difference in the fracture rates (alendronate, 5.0 percent [26/515]; risedronate, 3.8 percent [20/527]). This study was not designed to show a difference in the risk of osteoporotic fracture (the primary endpoint was hip trochanter BMD); any fractures occurring during the trial were reported simply as adverse events.

It is likely that a third bisphosphonate, ibandronate (Boniva), soon will vie with alendronate and risedronate for position on formularies. The U.S. Food and Drug Ad-

ministration approved a once-daily formulation of ibandronate in 2003, but it never was marketed — doubtless due to stiff competition presented by once-weekly products. Since then, more convenient formulations of ibandronate have been in development in the form of a once-monthly tablet and an intravenous formulation given every 2 or 3 months via a 15- to 30-second injection. A supplemental new drug application for once-monthly ibandronate was submitted to the FDA in May 2004, and an NDA for the intravenous formulation was submitted in December 2004. In addition, a once-yearly formulation of zoledronic acid, which also would be administered intravenously, is in phase 3 trials for treatment of osteoporosis. Both the once-monthly ibandronate tablet (Miller 2004) and the single yearly dose of zoledronic acid (Reid 2002) have been shown to increase BMD and change biochemical markers of bone turnover to an extent similar to that achieved with daily oral bisphosphonate treatment.

A best-practice formulary also would include either zoledronic acid or the less-expensive generic pamidronate for cancer patients. Zoledronic acid offers a greater range of indications and a shorter infusion time. Health plans will have to decide whether the increase in patient turnover achieved with zoledronic acid in clinical settings is sufficient to offset its higher cost.

Conclusion

Bisphosphonates have been designated as a key drug type for Part D formularies under MMA. It would be reasonable for a formulary to include either alendronate or risedronate, if not both, for the benefit of patients with osteoporosis or Paget's disease, and zoledronic acid or pamidronate for patients with cancer-related bone disorders. Health plans concerned about containing the costs of these agents should use risk-assessment strategies that place patients' BMD measurements in the context of other risk factors for osteoporotic fracture, so as to direct bisphosphonate treatment toward patients at the highest risk. Such a strategy would be in keeping with the aims of a new HEDIS measure to improve management of Medicare patients with osteoporosis.

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