THERAPY CLASS REVIEW

Getting to Zero Waste

2008 DRUG TREND REPORT

EXPRESS SCRIPTS®

Therapy Class Review

Going forward from this year's edition of the *Drug Trend Report,* drug classes formerly identified as "nonspecialty" will be designated as "traditional." Additionally, we have changed the therapy-class naming system from generic product identifier (GPI) codes to most common indication (MCI) numbers. A system proprietary to Express Scripts, MCIs identify classes by the main conditions they treat.

For 2008, we reviewed in depth the top seven traditional drug classes and the top three for specialty. These in-depth profiles give greater insight into cost and utilization trends as well as the factors influencing these trends in 2008. Additional information on "classes to watch" provides a glimpse into several traditional and specialty classes that affected trend in 2008 and that we feel will be important in 2009 and beyond.

TRADITIONAL

The top seven traditional classes, which accounted for nearly 50% of traditional spending, represent drugs used to treat some of the most common chronic diseases in the U.S.: high blood pressure, heart disease, diabetes, asthma and mental disorders. The top three traditional classes all treat metabolic syndrome, a cluster of conditions, such as abdominal obesity and insulin resistance, that often occur together, increasing the risk of heart disease, stroke and diabetes. Drugs to treat metabolic syndrome represented close to one-third of total traditional per member per year (PMPY) spend in 2008.

EXHIBIT 13

Percentages of Total Spend and PMPY Cost Change for Selected Traditional Therapy Classes 2007 to 2008

Therapy Class	Percentage of Total Spending	Percent Change in PMPY Cost
High Blood Cholesterol	9.1%	-8.0%
High Blood Pressure/Heart Disease	8.6%	-3.0%
Diabetes	8.0%	9.7%
Depression	7.0%	-0.9%
Ulcer Disease	6.3%	-5.2%
Asthma	5.6%	3.8%
Seizures	4.7%	13.7%
Pain	4.1%	11.4%
Mental/Neurological Disorders	3.3%	16.8%
Attention Disorders	2.8%	13.7%
Migraine Headaches	1.5%	10.5%
Bone Conditions	1.2%	-20.4%
Others	37.9%	1.2%
Total	**100.0%**	**1.5%**

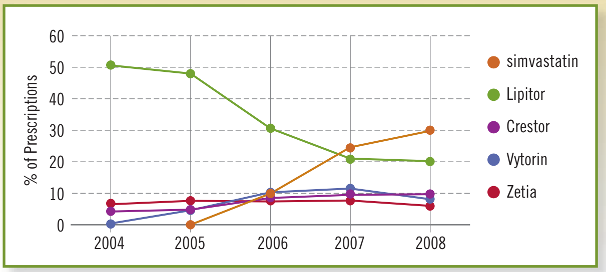
High Blood Cholesterol

Traditional Rank 1

Overall Trend -8.0%

Cost/Rx	**-10.2%**
Price	-5.8%
Units/Rx	0.1%
Brand/Generic Mix	-0.7%
Therapeutic Mix	-4.2%
Utilization	**2.5%**
Prevalence	2.4%
Intensity	0.1%
New Drugs	**0**

Market-Share Trend



Top Brand Drugs

Lipitor® Vytorin®
Crestor® Zetia®

Top Generic Drugs

simvastatin lovastatin
pravastatin gemfibrozil

Year in Review

- Following a 9% drop in 2007, overall trend in the high cholesterol class continued to be negative, driven by a 10% decrease in cost trend as patients moved to less expensive generic medications.
- Negative publicity surrounding the ENHANCE trial in early 2008 continued to result in a market share shift from Vytorin and Zetia to other agents, including simvastatin.
- Lipitor's market share stayed relatively steady from 2007 to 2008 as a result of its addition to formularies in mid-2007.

A Closer Look

After the ENHANCE study findings were released, Express Scripts evaluated the usage patterns for patients on Vytorin and found that 29% switched to another statin during the year and 17% stopped altogether.

What's Ahead

- Statins will continue to be the mainstay of cholesterol treatment. Growth in this category will be driven by brand promotion and new indications.
- Manufacturers are developing products that combine a statin with another type of cholesterol-lowering drug to reduce cholesterol in more than one way. Some of these products include Pravafen (pravastatin and fenofibrate), TriLipix™ and Crestor, and atorvastatin and ezetimibe.
- Following a patent settlement, generics for Lipitor are now expected late in 2011.
- Development of CTEP inhibitors, drugs that raise HDL cholesterol significantly, continues at a slower pace due to questions raised following the discontinuation of the lead product, torcetrapib.

Key Facts

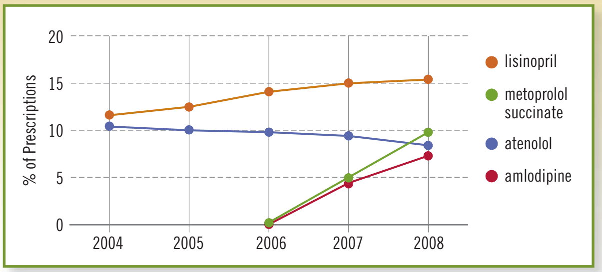
Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$68.68	1.23	11.4%	$55.83	9.7

High Blood Pressure/Heart Disease

Overall Trend -3.0%

Cost/Rx	**-4.7%**
Price	3.8%
Units/Rx	0.1%
Brand/Generic Mix	-9.0%
Therapeutic Mix	0.8%
Utilization	**1.4%**
Prevalence	1.7%
Intensity	-0.3%
New Drugs	**0.3%**

Market-Share Trend



Top Brand Drugs

Diovan®
Cozaar®
Diovan HCT®
Benicar®

Top Generic Drugs

lisinopril
atenolol
metoprolol succinate
amlodipine

Year in Review

- This category now includes all medications for treating high blood pressure, including antihypertensives (ACE inhibitors and angiotensin receptor blockers), beta blockers and calcium channel blockers. In previous years, these classes were reported separately.
- The high blood pressure class is dominated by generics, which account for eight of the top 10 products.
- The 2007 approvals of generics for Altace,® Coreg,® Lotrel,® Norvasc® and Toprol-XL® continued to drive down cost trend.
- In 2008, first-time generics were launched for Inspra® and Sular.® However, a new formulation of Sular helped to limit generic erosion of the brand product.

A Closer Look

Although this drug class is dominated by generic medications, opportunities that include the implementation of Step Therapy still exist for clients to manage costs appropriately. Express Scripts found that clients with Step Therapy targeting drugs in the class saw a 3.6-fold lower trend rate. Clients with Step therapy had a -4.3% trend compared to a -1.2% trend without Step Therapy.

What's Ahead

- A shortage of metoprolol succinate extended release (generic Toprol-XL) caused a shift back to the brand or to other beta blockers in early 2009.
- In 2009, generics to Aceon® and Cardizem® LA are expected.
- The expiration of the Cozaar patent in 2010 will bring to market the first generic in the angiotensin receptor blocker (ARB) class of medications.
- Following a patent settlement, generics to Caduet® are now likely in late 2011.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$65.29	2.16	15.4%	$30.21	12.8

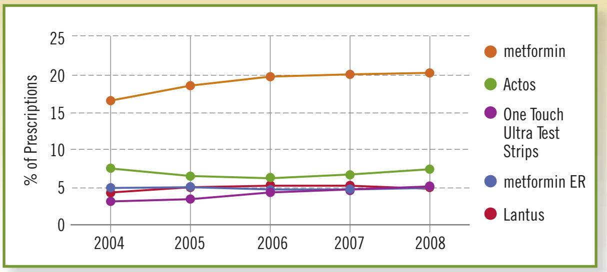
Diabetes

Traditional Rank 3

Overall Trend 9.7%

Cost/Rx	**7.9%**
Price	5.1%
Units/Rx	1.0%
Brand/Generic Mix	-0.1%
Therapeutic Mix	1.7%
Utilization	**1.6%**
Prevalence	2.1%
Intensity	-0.5%
New Drugs	**0**

Market-Share Trend



Top Brand Drugs

Actos®
Lantus®
One Touch® Ultra® Test Strips
Januvia®

Top Generic Drugs

metformin
glimepiride
metformin extended release
glyburide

Year in Review

- 2008 is the first year that diabetic supplies (meters, test strips and syringes), which typically do not require a prescription although they are covered under many prescription-drug plans, were included in the diabetes category. However, prescription drugs represent 85% of spend.
- In 2007, the American Diabetes Association (ADA) released a position paper "Standards of Medical Care in Diabetes," supporting the use of generic metformin early in the management of type 2 diabetes, likely contributing to its increased use.
- The continued impact of safety concerns resulted in movement from Avandia® to other brands, moderating utilization intensity (the number of prescriptions per utilizer).

A Closer Look

The 2007 ADA guideline changes were expected to increase the number of patients taking two drugs for diabetes. However, when Express Scripts researchers examined patterns of use over 2007 and 2008 and found only modest changes in patients with multiple monthly claims for antidiabetic drugs. In 2007, approximately 54% of patients taking an antidiabetic agent were paying only one copayment in the class. That percentage of users increased slightly to 56% in 2008.

What's Ahead

- The incidence of diabetes continues to rise as the population ages and obesity is more prevalent.
- Cost trend in this category will continue to increase as new brand products are approved and first-time generics have very limited impact.
- Alogliptin and Onglyza™ (saxagliptin), rivals for Januvia, are currently under FDA review with action dates in the middle of 2009.
- Victoza® (liraglutide), a once-daily Byetta® competitor, could enter the market in 2009.
- In 2010, the market could see the introduction of once-weekly Byetta LAR, followed by a similar new product, currently known as R1583, the following year.
- Although the market withdrawal of Exubera® resulted in discontinuation of development for many other inhaled insulins, one product, Afresa,® continues in late-stage trials. It could reach the market as early as 2010 unless safety-related questions delay its release.
- Significant generic opportunities are limited until the thiazolidinediones (TZDs), Actos and Avandia, face patent expiration early next decade.

Key Facts

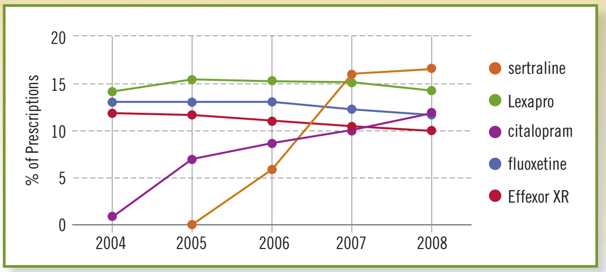
Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$60.54	0.84	4.8%	$71.99	16.2

Depression

Overall Trend -0.9%

Cost/Rx	**-1.9%**
Price	-1.0%
Units/Rx	0.5%
Brand/Generic Mix	-1.6%
Therapeutic Mix	0.2%
Utilization	**0.6%**
Prevalence	0.1%
Intensity	0.5%
New Drugs	**0.4%**

Market-Share Trend



Top Brand Drugs

Lexapro® Cymbalta®
Effexor XR® Wellbutrin XL®

Top Generic Drugs

sertraline fluoxetine
citalopram paroxetine

Year in Review

- Overall trend for antidepressants was negative as more patients used generics.
- In 2008, first-time generics to Paxil CR® and Wellbutrin XL 150mg tablets were introduced.
- New products, Pristiq® and venlafaxine extended-release tablets, became available as alternatives among the selective serotonin and norepinephrine reuptake inhibitors (SNRIs).
- Market share for Cymbalta is increasing due to its new indications for diabetic neuropathic pain and generalized anxiety disorder (GAD).

A Closer Look

- One significant factor driving trend lower in this category was increased use of generic medications. While the introduction of generics for popular brands helped to move utilization away from brands, clients who actively managed trend in this category through the adoption of Step Therapy saw their trend go even lower than the overall -0.9% trend. Clients using Step Therapy for antidepressants had a negative 2.5% trend compared to an increase of 2.2% in trend for clients without Step Therapy.
- Utilization trends were more moderate in 2008 after the 3.1% utilization trend in 2007. However, different patterns across age groups were noted with patients 64 years of age and younger showing negative utilization trends, while those 65 and older saw utilization increases of 6%.

What's Ahead

- Generic selective serotonin reuptake inhibitors (SSRIs) will continue to be the most commonly used antidepressants.
- Treatment of pain and other new indications for the SNRIs will help maintain their market shares.
- Agomelatin, the first antidepressant that targets both melatonin receptors and serotonin receptors, could reach the market in 2009.
- First-time AB-rated generics to Effexor XR capsules are expected in July 2010.
- The drug patent on Lexapro, the brand with the highest market share in the class, expires in March 2012.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$52.89	0.84	9.7%	$62.53	8.2

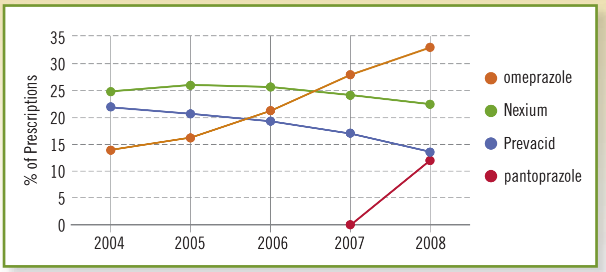
Ulcer Disease

Traditional Rank 5

Overall Trend -5.2%

Cost/Rx	**-9.5%**
Price	-4.8%
Units/Rx	1.3%
Brand/Generic Mix	-3.2%
Therapeutic Mix	-3.0%
Utilization	**4.7%**
Prevalence	3.7%
Intensity	1.0%
New Drugs	**0**

Market-Share Trend



Top Brand Drugs

Nexium® AcipHex®
Prevacid® Prilosec OTC®

Top Generic Drugs

omeprazole ranitidine
pantoprazole famotidine

Year in Review

- Although utilization for ulcer drugs increased, overall trend was negative due to a large cost decrease as more patients used generic drugs.
- In late 2007, pantoprazole (generic Protonix) reached the market through an at-risk launch, before patent litigation was resolved. The brand manufacturer quickly introduced an authorized generic and supplies of both remained available throughout 2008. The significantly higher cost of pantoprazole compared to omeprazole will require innovative management strategies within the generic category.
- In addition, first-time generics were launched for Prilosec® 40mg and Prilosec OTC.®

A Closer Look

Utilization trends continue to be strong for this class. At 4.7%, it has one of the highest utilization trends among the top seven drug classes. While patent expirations continue to shift market share in favor of generics, clients can move the needle even further. Clients that adopted Step Therapy saw a 3-fold greater trend decrease (-6.6%) for this class than clients that did not implement Step Therapy (-2.1%).

What's Ahead

- Continuing availability of generic Protonix is uncertain. Existing supplies will diminish, but another at-risk launch or patent invalidation could keep pantoprazole on the market before the patent for Protonix expires in 2011.
- Kapidex,™ a follow-on to Prevacid, was marketed in February 2009 in anticipation of patent expiration for Prevacid in November 2009.
- As the proton pump inhibitor (PPI) class begins to mature, more products will become available over-the-counter (OTC). In 2009, both Prevacid and Zegerid® could be made available as OTC formulations.

Key Facts

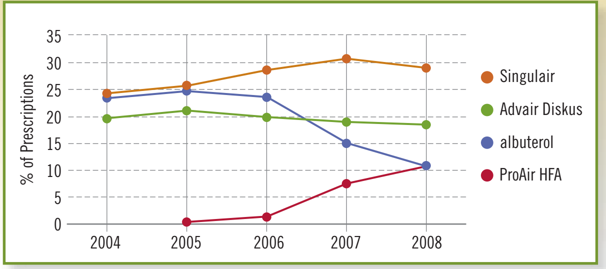
Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$47.64	0.61	7.9%	$77.55	7.1

Asthma

Overall Trend 3.8%

Cost/Rx	**5.8%**
Price	6.0%
Units/Rx	0.3%
Brand/Generic Mix	-0.6%
Therapeutic Mix	0.1%
Utilization	**-1.8%**
Prevalence	0.7%
Intensity	-2.5%
New Drugs	**0**

Market-Share Trend



Top Brand Drugs

Singulair® ProAir® HFA
Advair Diskus® Flovent® HFA

Top Generic Drugs

albuterol theophylline

Year in Review

- Patients transitioned from generic albuterol inhalers to more expensive brand albuterol inhalers that use hydrofluoroalkane (HFA) propellants after the FDA phased out ozone-damaging chlorofluorocarbon (CFC) propellants in older inhalers.
- Together, Singulair and Advair Diskus now represent 47% of market share in this category.

A Closer Look

Utilization trends for 2008 were negative, driven by a reduction in the number of prescriptions rather than in the number of patients using asthma medication. Asthma is the most common chronic condition in children and utilization is expected to grow. A study published in the November 2008 issue of the journal *Pediatrics* by Express Scripts researchers found that the growth rate in the prevalence of these agents increased 47% from 2002 to 2005.

What's Ahead

- Because of difficulty in reproducing complex inhalation devices, generic asthma inhalers are not expected in the near term.
- Once-daily indacaterol, currently under FDA review, could provide an alternative to twice-daily Foradil® Aerolizer® and Serevent® Diskus.® Indacaterol is administered in a dry-powder inhaler.
- Additional products that combine corticosteroids and beta agonists will compete in the asthma-controller market. A formoterol and mometasone inhaler may enter the market in 2010 and a follow-on to Advair is also expected.
- Although AB-rated generics to Advair are not probable, alternative brand products are likely — beginning in 2011.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$42.23	0.45	8.0%	$93.13	5.2

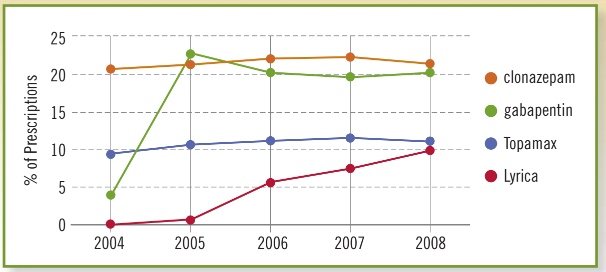
Seizures

Traditional Rank 7

Overall Trend 13.7%

Cost/Rx	**6.6%**
Price	8.1%
Units/Rx	0.6%
Brand/Generic Mix	-4.8%
Therapeutic Mix	2.9%
Utilization	**6.7%**
Prevalence	5.9%
Intensity	0.7%
New Drugs	**0**

Market-Share Trend



Top Brand Drugs

Topamax®
Lyrica®
Lamictal®
Depakote® ER

Top Generic Drugs

clonazepam
gabapentin
lamotrigine
phenytoin extended release

Year in Review

- Utilization increases are due, in part, to non-seizure indications, such as fibromyalgia, for many drugs in this class.
- In 2008, first-time generics to Depakote,® Lamictal and Keppra® helped mitigate overall cost trend. The full effect of these generics will be observed in 2009.

A Closer Look

For the seizures class, both utilization and costs trends were driven by three drugs — Topamax, Lyrica and Lamictal — with varying patterns of trend increases across the three agents. Together they accounted for 49.4% of total cost in the class. The growth in Lyrica was driven by a 36% increase in utilization and a 9% increase in cost/Rx growth; Topamax trends were 5% for utilization and 11% cost/Rx while Lamictal cost trend was driven by a 15% growth in utilization.

What's Ahead

- Cost savings are expected with the 2009 availability of generics to Depakote ER and Topamax.
- New brands, Banzel™ (FDA-approved in November 2008) and Vimpat® (approved in February 2009) will provide additional treatment options for epilepsy patients.
- Several additional drugs that are in development include Rikelta™ (brivaracetam), Comfyde™ (carisbamate), Stedesa™ (eslicarbazepine) and retigabine. These products will provide treatment alternatives for patients with epilepsy.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$35.70	0.31	3.9%	$113.72	7.6

Pain

Traditional Rank 9

Overall Trend	11.4%
Cost/Rx	8.6%
Utilization	2.6%
New Drugs	0

Top Brand Drugs

OxyContin®

Top Generic Drugs

hydrocodone and acetaminophen
oxycodone and acetaminophen
tramadol

Year in Review

- The pain class includes narcotic analgesics, salicylates and narcotic combination products. Non-steroidal anti-inflammatory drugs (NSAIDs) are in a separate class.
- Generic products are highly utilized in the pain category. However, many higher priced brands also compete for market share.
- Patent settlements allowed generic OxyContin (oxycodone controlled release) to remain on the market through 2008.

What's Ahead

- Supplies of generic OxyContin will diminish throughout 2009, allowing re-establishment of brand-only OxyContin.
- New abuse-resistant formulations of the long-acting opioids are in development. These products include Embeda™ (morphine and naltrexone extended-release tablets) and abuse-resistant OxyContin, which could reach the market in 2009 and 2010, respectively.
- Tapentadol, a synthetic analgesic with dual actions as a mu opioid receptor agonist and a norepinephrine reuptake inhibitor, likely will be launched in 2009 for the treatment of moderate to severe acute pain.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$30.79	0.74	17.6%	$41.81	7.4

Mental/Neurological Disorders

Traditional Rank 10

Overall Trend	16.8%
Cost/Rx	9.8%
Utilization	6.4%
New Drugs	0

Top Brand Drugs	Top Generic Drugs
Seroquel®	amitriptyline
Aricept®	nortriptyline
Namenda®	lithium

Year in Review

- Drugs in the mental/neurological disorders class treat Alzheimer's disease, anxiety, bipolar disorder, psychoses, and other organic brain disorders.
- While cost trend went up due to price increases and switching to more expensive medications, it was also tempered by the first-time availability of generics to Risperdal® in June 2008.
- Atypical antipsychotics represent over 75% of the total cost in this category. These drugs are used extensively off label. Additionally, a growing number of primary care physicians (PCPs) are prescribing them. While 17% of prescriptions for atypical antipsychotics were written by PCPs in 2006, the percentage increased to 24% in 2008.

What's Ahead

- New brand antipsychotic drugs that could begin competing for market share in 2009 and 2010 include Fanapta™ (iloperidone), Serdolect® (sertindole) and Saphris™ (asenapine).
- Generics to the Alzheimer's drug, Aricept, could be available as early as November 2010.
- The next atypical antipsychotic drug due to lose patent protection is Zyprexa® in October 2011.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$24.87	0.13	1.7%	$185.04	7.4

Attention Disorders

Traditional Rank 12

Overall Trend	13.7%
Cost/Rx	7.6%
Utilization	5.6%
New Drugs	0

Top Brand Drugs

Adderall XR ™
Concerta®
Strattera®

Top Generic Drugs

amphetamine salt combination
methylphenidate
dextroamphetamine

Year in Review

- Vyvanse,™ launched in 2007, has been gaining market share at the expense of Adderall XR.
- Although over 50% of drug use in this category is for children 19 years of age and younger, utilization continues to grow among young adults. For patients in their 20s and 30s, utilization increased 17.5% in 2007 and 15.7% in 2008. Utilization trend for children up to age 19 was 5% in 2007; with flat growth (0.9%) in 2008.

What's Ahead

- The first generic to Adderall XR was released in April 2009.
- The availability of generic Concerta remains in question due to ongoing litigation and concerns raised by a Citizen's Petition.
- Intuniv™ (guanfacine extended release) could receive approval in late 2009. As a centrally acting alpha-2 noradrenergic agonist, immediate-release guanfacine is already approved for treating hypertension. Intuniv represents a new option for the treatment of ADHD.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$21.14	0.16	2.1%	$130.15	9.0

Migraine Headaches

Traditional Rank 19

Overall Trend	10.5%	Top Brand Drugs	Top Generic Drugs
Cost/Rx	14.3%	Imitrex®	isometheptene, dichloralphenazone and acetaminophen
Utilization	-4.9%	Zomig®	sumatriptan
New Drugs	1.8%	Relpax®	

Year in Review

- Brand triptan drugs dominate the migraine class with over 85% of the market.
- Injected and tablet forms of sumatriptan, generics to the first triptan, Imitrex, were launched late in 2008. They will have an impact on 2009 trend.
- The new combination drug Treximet,® a single-pill combination of sumatriptan and naproxen, was approved in April 2008.

What's Ahead

- Supplies of generic Imitrex began increasing early in 2009.
- Other first-time generic triptans that could enter the market are naratriptan (generic Amerge®) in 2010 and rizatriptan (generic Maxalt®) in 2012.
- Exclusivity for Treximet expires in 2011, the earliest possible launch date for its generics.
- Telcagepant, the first drug in a new class known as calcitonin gene-related peptide (CGRP) receptor antagonists, could be approved to treat migraine headaches in 2010. In clinical trials, telcagepant had fewer cardiovascular side effects than are seen with the triptans.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$11.42	0.06	1.3%	$187.02	4.3

Bone Conditions

Traditional Rank 21

Overall Trend	-20.4%	Top Brand Drugs	Top Generic Drugs
Cost/Rx	-17.4%	Actonel®	alendronate
Utilization	-3.6%	Boniva®	
New Drugs	0	Fosamax Plus D™	

Year in Review

- Cost trend for bone conditions decreased dramatically following the introduction of generics to Fosamax, the first bisphosphonate, in February 2008.
- Utilization also decreased as fewer patients used bisphosphonates. The transition of some patients from the daily or weekly oral bisphosphonates to a specialty drug, once-yearly intravenous Reclast,® may be partly responsible.

What's Ahead

- The specialty drug denosumab (D-mab) could be approved late 2009. As a twice-yearly subcutaneous injection, denosumab could transfer more market share away from traditional-drug spend into a specialty class.
- The next bisphosphonate to face patent expiration is Boniva, which could have generic competition as early as 2012.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$9.24	0.17	1.7%	$55.73	8.5

SPECIALTY

Following are detailed analyses of the three top specialty classes, which accounted for nearly 64% of specialty spend in 2008. Classes to watch include those that had significant impact on 2008 specialty trend. Six of the top eight specialty therapy classes grew at double-digit rates, with PMPY spending for drugs used to treat pulmonary hypertension increasing 59%. Looking closer into the components of these trends will be important as managing specialty drug spending remains a key priority for many clients.

EXHIBIT 14

Percentages of Total Spend and PMPY Cost Change for Selected Specialty Therapy Classes 2007 to 2008

Therapy Class	Percentage of Total Spending	Percent Change in PMPY Costs
Inflammatory Conditions	27.5%	17.0%
Multiple Sclerosis	20.2%	18.3%
Cancer	16.0%	18.6%
Growth Deficiency	5.2%	20.3%
Blood Cell Deficiency	4.3%	-11.4%
Respiratory Conditions	3.2%	-0.2%
Hepatitis C	2.9%	-7.3%
Pulmonary Hypertension	2.7%	59.2%
Others	18.0%	16.8%
Total	**100.0%**	**15.4%**

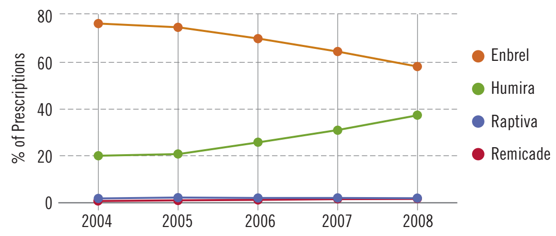
Inflammatory Conditions

1 Specialty Rank

Overall Trend 17.0%

Cost/Rx	**5.7%**
Price	5.9%
Units/Rx	-0.6%
Brand/Generic Mix	0
Therapeutic Mix	0.4%
Utilization	**10.5%**
Prevalence	9.2%
Intensity	1.2%
New Drugs	**0.2%**

Market-Share Trend



Top Brand Drugs

Enbrel®
Humira®
Raptiva®
Remicade®

Top Generic Drugs

None

Year in Review

- Expanded indications and earlier use of tumor necrosis factor (TNF) inhibitors (Enbrel, Humira and Remicade) to treat rheumatoid arthritis (RA) continue to drive trend growth.
- Due in part to its 2007 approval for Crohn's disease, Humira continued to make market-share gains on Enbrel, the market leader in the class.
- Cimzia,® a long-acting TNF inhibitor that is administered as a once-monthly subcutaneous (SQ) injection, was approved for Crohn's disease in April 2008.

A Closer Look

- Utilization growth among drugs to treat inflammatory conditions is being driven by both better channel management — moving reimbursement from the medical benefit to the pharmacy benefit — and expanded indications for many of the agents in the class.
- CuraScript works with clients to manage out waste in this high-use class. For instance, clinical guidelines help physicians determine appropriate dosages for anti-inflammatory agents. After implementing guidelines, one CuraScript client realized significant savings from an 11% reduction in inappropriate utilization.

What's Ahead

- Cimzia is expected to gain market share in 2009 due to increased use for Crohn's disease and probable approval of an expanded indication for RA.
- In 2009, Simponi™ (golimumab), another long-acting TNF inhibitor, is expected to be approved by the FDA for RA, ankylosing spondylitis and psoriatic arthritis. Like Cimzia, Simponi is a monthly SQ injection that will be more convenient than Enbrel and Humira, which require more frequent dosing.
- In late 2009, Stelara™ (ustekinumab), a novel biologic drug that works by inhibiting interleukins 12 and 23, may be approved in the US to treat psoriasis.
- Several drugs, including LymphoStat-B® (belimumab), which are in development for the treatment of lupus, may be approved by the end of the decade.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$27.17	0.02	0.18%	$1,633.01	8.3

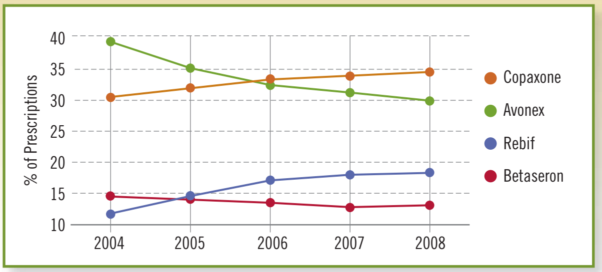
Multiple Sclerosis

Specialty Rank 2

Overall Trend 18.3%

Cost/Rx	**21.9%**
Price	23.5%
Units/Rx	-0.2%
Brand/Generic Mix	0
Therapeutic Mix	-1.1%
Utilization	**-2.9%**
Prevalence	-1.0%
Intensity	-1.9%
New Drugs	**0**

Market-Share Trend



Top Brand Drugs

Copaxone®
Rebif®
Avonex®
Betaseron®

Top Generic Drugs

None

Year in Review

- Although utilization decreased slightly in 2008, cost/Rx growth continues to be a major driver of trend for drugs to treat multiple sclerosis (MS). Double-digit price inflation was seen for six of the seven MS drugs driving the class to 24% price inflation.
- Copaxone, a daily non-interferon, was the market leader. Primarily taking market share from Avonex, an interferon that is used weekly, Copaxone is associated with fewer flu-like symptoms than Avonex and other interferons such as Rebif and Betaseron.

A Closer Look

- While price inflation for MS drugs increased 24%, copayments per prescription went up by only 45 cents. Member share of total costs in the class actually decreased from 2.4% to 2%.
- Utilization decreased by nearly 3%, partly due to side effects from the drugs. Because MS drugs delay disease progression rather than improve function, patient perceptions of treatment effectiveness also affect utilization. In a study presented at the 2009 American Academy of Neurology annual meeting, Express Scripts researchers found that only 22% of patients believed that the benefits received from taking MS medication were worth the costs.

What's Ahead

- Current MS therapies are injected, but several oral drugs for MS, including fingolimod, Panaclar™ and teriflunomide, are in late-phase development.
- Cladribine tablets may be the first disease-modifying oral drug to receive FDA approval for MS.
- Another oral drug, Fampridine SR, may be approved in late 2009 for treatment of symptomatic MS, despite an FDA request for more information from the manufacturer.
- Some oral therapies may be used in combination with currently available injectable drugs, and they also may be used earlier in the course of MS.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$20.00	0.01	0.10%	$2,006.43	9.5

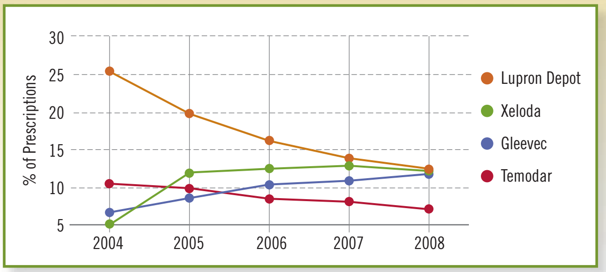
3 Specialty Rank

Cancer

Overall Trend 18.6%

Cost/Rx	**15.7%**
Price	10.6%
Units/Rx	-0.7%
Brand/Generic Mix	0
Therapeutic Mix	5.3%
Utilization	**2.0%**
Prevalence	0.9%
Intensity	1.0%
New Drugs	**0.7%**

Market-Share Trend



Top Brand Drugs

Lupron Depot® Gleevec®
Xeloda® Temodar®

Top Generic Drugs

methotrexate injection
leuprolide

Year in Review

- Cost/Rx was the primary influence on cancer trend growth in 2008.
- Utilization continues a shift to new brands, driving up cost for cancer treatment.
- After contributing 2.8% to trend in 2007, however, new drugs had a much smaller effect on cancer trend in 2008. No new blockbuster medications for cancer were approved in 2008.

A Closer Look

To address adherence, complexity and cost issues associated with oral specialty medications for cancer, CuraScript piloted an oral oncology specialty care management program with two large Blue Cross Blue Shield plans in 2008. Focused on preventing disease progression, the program provides clinical care counseling, side effect management and proactive monitoring for patients using oral anticancer therapy.

What's Ahead

- The cancer pipeline is extensive, accounting for approximately half of all specialty drugs in development.
- Importantly, however, even the vast cancer-drug pipeline has significant hurdles to market entrance. The FDA often requires data on improved overall survival before approving new cancer medications.
- While many current cancer drugs and most in the pipeline are administered by intravenous (IV) infusion, one-fourth of investigational cancer drugs are oral. Prescription-drug benefits are affected more by oral drugs than by IV drugs, which usually fall into medical benefits.
- Oral cancer drugs in late-phase development include Afinitor® (everolimus) for kidney cancer, deforolimus for bone and soft tissue sarcomas, phenoxodiol for ovarian cancer and abiraterone for prostate cancer.
- Therapeutic vaccines such as BiovaxID™ for non-Hodgkin's lymphoma and Provenge® for prostate cancer may enter the market within the next couple of years.
- Targeted therapies, such as the oral tyrosine kinase inhibitor Zactima™ (vandetanib) and the IV monoclonal antibodies Arzerra™ (ofatumumab) and HuMax-EGFr™ (zalutumumab), are expected to play an increasingly important role in the treatment of various cancer types.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$15.78	0.01	0.16%	$2,097.03	4.3

Growth Deficiency

Specialty Rank 4

Overall Trend	20.3%
Cost/Rx	6.5%
Utilization	12.9%
New Drugs	0

Top Drugs

Humatrope®
Nutropin AQ®
Genotropin®
Norditropin NordiFlex®

Year in Review

- A new, easier-to-administer pen cartridge of the follow-on biologic growth hormone Omnitrope® was approved in September 2008.
- Accretropin™ is a recombinant human growth hormone that was approved in early 2008, but not yet launched on the U.S. market.
- Clients with prior authorization (PA) in place to manage age-appropriate utilization found that only 21% of utilization was for patients over the age of 25 compared to 32% for clients without PA in place.

What's Ahead

- While market share of Omnitrope has been minimal since its launch in early 2007, it will continue to grow with the availability of the new pen formulation.
- Tesamorelin, a growth hormone-releasing factor analog, may be approved in 2009 for HIV-related lipodystrophy.
- ALTU-238, a long-acting human growth hormone that is administered once monthly, is not expected to be approved until 2012.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$5.16	Less than 0.01	0.02%	$2,646.61	7.9

Blood Cell Deficiency

Specialty Rank 6

Overall Trend	-11.4%
Cost/Rx	7.1%
Utilization	-17.3%
New Drugs	0.1%

Top Drugs

Procrit®
Aranesp®
Neupogen®
Neulasta®

Year in Review

- Safety concerns associated with erythropoiesis-stimulating agents (ESAs) — Aranesp, Epogen® and Procrit — resulted in decreased utilization for these anemia medications and possibly shifting reimbursement through medical benefits.
- Nplate™ and Promacta® are new medications for idiopathic thrombocytopenic purpura (ITP), a bleeding disorder related to low platelet counts.
- Mozobil,™ a drug used in combination with Neupogen to mobilize stem cells for transplantation, was approved in December 2008.

What's Ahead

- Following their approvals in the second half of 2008, Nplate and Promacta are expected to have a greater effect on cost in 2009 than in 2008.
- Approval of Hematide,™ a synthetic peptide-based ESA for anemia, is expected in 2010.
- Two additional oral medications for ITP (AKR-501 and fostamatinib) may be approved in the next few years.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$4.21	Less than 0.01	0.05%	$1,745.08	4.5

Respiratory Conditions

Specialty Rank 8

Overall Trend	-0.2%
Cost/Rx	8.8%
Utilization	-8.2%
New Drugs	0

Top Drugs

Xolair®
Pulmozyme®
TOBI®

Year in Review

- One reason that the use of medications for respiratory conditions decreased in 2008 is that fewer patients are taking Xolair, an injected biologic medication used to treat allergic asthma.
- While price inflation increased over 23%, clients absorbed the extra costs since copayments per prescription only increased by 45 cents. Member share of total costs in this category actually decreased from 2.4% to 2.0%.

What's Ahead

- In 2009, pirfenidone may be the first medication approved to treat idiopathic pulmonary fibrosis (IPF), a rare condition characterized by scarring of the lungs. IPF can lead to death as early as two years from the time of diagnosis. Pirfenidone is a biologic drug that is administered orally.
- Among several drugs that may be approved within the next couple of years for cystic fibrosis (CF) are denufosol and VX-770, which both improve mucus clearance for CF patients.
- If approved by the FDA, Cayston™ (aztreonam lysinate for inhalation) will compete with TOBI, another inhaled medication, for treating CF lung infections.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$3.14	Less than 0.01	0.02%	$2,354.33	7.2

Hepatitis C

Specialty Rank 9

Overall Trend	-7.3%
Cost/Rx	4.6%
Utilization	-11.4%
New Drugs	0

Top Drugs

Pegasys®	ribavirin
PegIntron® Redipen®	ribapak

Year in Review

- Declining use of hepatitis C medications may be due to the growing population of non-responders to currently available treatment options.

What's Ahead

- At least initially, many of the oral drugs that are in development for the treatment of hepatitis C will be used in combination with ribavirin and pegylated interferon.
- Oral protease inhibitors such as telaprevir and boceprevir are among the most promising drugs in the hepatitis C pipeline. Approval of these agents is not expected until 2011, however.
- Albuferon® and Locteron® are long-acting interferons that may be administered once every two weeks or once-monthly compared to weekly dosing with currently available interferons. Albuferon may be approved in 2010 while approval of Locteron is not expected until 2012.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$2.86	Less than 0.01	0.02%	$1,171.00	10.1

Pulmonary Hypertension

Specialty Rank 10

Overall Trend	59.2%
Cost/Rx	17.0%
Utilization	36.1%
New Drugs	0

Top Drugs

Revatio®
Tracleer®
Letairis®

Year in Review

- At almost 60%, drug trend for pulmonary hypertension (PH) was the third highest for all specialty therapy classes. Large increases in both cost/Rx and utilization contributed to the rise.
- In 2008, Tracleer — an endothelin receptor antagonist (ERA) — lost market share to a similar agent, Letairis. Approved in mid-2007, Letairis may be associated with less liver toxicity and fewer drug interactions than Tracleer. It is also indicated for use earlier in the disease.
- Revatio (sildenafil, the same drug as Viagra®) is a phosphodiesterase type-5 (PDE5) inhibitor that relaxes muscles in the lungs. FDA approved in June 2005, Revatio represented over 50% of PH prescriptions in 2008.

What's Ahead

- Tyvaso, an inhaled form of treprostinil, is likely to be approved for PH in April 2009. For use in combination with other oral PH drugs, Tyvaso requires four inhalations per day compared to as many as nine inhalations per day for its already approved competitor, Ventavis.®
- Approval of a second PDE5 inhibitor Adcirca® (tadalafil, the same drug as Cialis®) for PH is expected in May 2009. Adcirca may capture market share from Revatio because it requires less frequent administration (once-daily versus three times daily).
- Thelin,® a third ERA, may also be approved in 2009.

Key Facts

Cost PMPY	# Rx PMPY	Prevalence of Use	Average Cost/Rx	# Rx/User/Year
$2.68	Less than 0.01	0.01%	$2,846.36	9.3