

# New Products Expected to Come to Market Between 2003 and 2007

## Gastrointestinal (GI)

Biologic products will begin to make a greater impact in the treatment of Crohn's disease. Antegren® is a humanized monoclonal antibody designed to bind to receptors on white blood cells, altering their response to and involvement in the inflammatory process. This drug is being studied for a variety of diseases with an inflammatory component, including Crohn's disease and multiple sclerosis (MS). Humicade™, a monoclonal antibody that blocks the effects of Tumor Necrosis Factor alpha (TNF-alpha), is also under investigation for the treatment of both Crohn's disease and rheumatoid arthritis (RA). Once approved, these agents will compete with Remicade®, which is currently the only biologic agent approved for the treatment of Crohn's disease.

In 2002, the FDA approved the marketing of Zelnorm® and the re-introduction of Lotronex® for the treatment of irritable bowel syndrome (IBS). However, with approximately 50 million Americans believed to suffer from IBS, its treatment remains a relatively untapped market. Dextroglumide and renzapride are being studied for the treatment of constipation-predominant IBS, while cilansetron is being evaluated for the treatment of the diarrhea-predominant type of the disease. The FDA may be cautious with the approval of these products following the withdrawal and eventual re-introduction of Lotronex®.

Emend® is a substance p inhibitor for the treatment of chemotherapy-induced nausea and vomiting. Clinical trials have indicated that when used in combination with other anti-emetics, Emend® may be effective for the treatment of both acute and delayed nausea and vomiting. If FDA review proceeds as planned, this drug should reach the market in 2003.

BRAND NAME	GENERIC NAME	PROPOSED USE	EXPECTED RELEASE DATE				
			2003	2004	2005	2006	2007
Antegren®	natalizumab	Crohn's disease		x			
Emend®	aprepitant	Nausea, vomiting	x				
	dextroglumide	IBS			x		
	cilansetron	IBS			x		
	renzapride	IBS					x
Humicade™	CDP-571	Crohn's disease		x			

### Patent Expirations:

- Zofran® 2005
- Protonix® 2006 (extension likely)

## Central Nervous System (CNS)

In 2003, three additional medications for the treatment of erectile dysfunction (ED) may enter the U.S. prescription market. Cialis® and Levitra®, oral medications that are currently under FDA review, have a mechanism of action similar to Viagra®. However, they are more selective for the phosphodiesterase 5 enzyme (which may result in fewer side effects), and they have a longer duration of action. Uprima® is a dopamine receptor agonist that is administered sublingually (under the tongue). Since it has a different mechanism of action, it has the potential to work in patients who are unresponsive to the other therapies.

The treatment of depression is another significant focus for medication development. Cymbalta® is a norepinephrine and serotonin re-uptake inhibitor for the treatment of depression and, at a different dose, for the treatment of stress urinary incontinence. Gepirone ER is a 5-HT1a agonist for the treatment of major depression and major depression with anxiety. However, the FDA is requiring additional studies to support marketing approval, delaying potential approval until at least 2004. Aprepitant is also being studied as an antidepressant, but limited efficacy data are available at this time.

The sedative/hypnotic market will see some additional growth in the upcoming years. Estorra™ is under development for the treatment of transient and chronic insomnia. It is an isomer of zopiclone, a hypnotic agent available only outside of the U.S. Indiplon is a GABA agonist/non-benzodiazepine sedative/hypnotic for treatment of chronic insomnia. It is being looked at in both rapid-release and modified-release formulations to help initiate and maintain sleep.

Pregabalin is a follow-on compound to Neurontin®. It is being studied for many diseases, including epilepsy, general anxiety disorder (GAD) and neuropathic pain. Development of this drug was temporarily delayed due to concerns about carcinogenicity in animal studies.

BRAND NAME	GENERIC NAME	PROPOSED USE	EXPECTED RELEASE DATE				
			2003	2004	2005	2006	2007
Cymbalta®	duloxetine	Depression, urinary incontinence	x				
Cialis®	tadalafil	Erectile dysfunction	x				
Levitra®	vardenafil	Erectile dysfunction	x				
Uprima®	apomorphine	Erectile dysfunction	x				
	memantine	Alzheimer's disease		x			
Zomaril™	iloperidone	Psychosis		x			
Estorra™	eszopiclone	Hypnotic		x			
	pregabalin	Epilepsy, GAD, neuropathic pain			x		
	rimonabant	Obesity			x		
	gepirone ER	Depression		x			
	aprepitant	Depression			x		
	Org-5222	Psychosis					x
	indiplon	Hypnotic			x		

### Patent Expirations:

- Neurontin® key patent expired (ongoing litigation), competition possible 2003
- Wellbutrin SR®/Zyban® patent expired (generics awaiting appellate ruling/FDA approval)
- Serzone® 2003
- Paxil® 2003 (ongoing litigation)
- Celexa® 2004
- Zolof® 2006
- Imitrex® 2007
- Ambien® 2007

## Respiratory

Xolair™ is a monoclonal antibody that binds and inhibits the effects of IgE antibodies, which are immune system proteins involved in the inflammatory process that produces many symptoms of allergic asthma. This product may be limited to the treatment of severe, refractory asthma because it likely will require a monthly injection in a clinic setting. A product with a similar mechanism of action is TNX-901, which is being developed to provide protection against reactions to unintentional peanut ingestion by people who have severe allergies to peanuts.

With initiatives to comply with the Montreal Protocol by phasing out the use of all chlorofluorocarbons (CFCs), some of the currently available metered dose inhalers used to treat asthma eventually will be removed from the market. Therefore, the additional CFC-free products under development will increase therapeutic options for people with asthma. Ciclesonide and Asmanex® are both CFC-free inhaled corticosteroids for the maintenance treatment of asthma. Spiriva® is a longer-acting version of the drug in Atrovent®. Therapy with Spiriva® would require a once-daily administration, compared to four times a day with Atrovent®.

A new class of oral medications known as phosphodiesterase 4 (PDE4) inhibitors may provide anti-inflammatory and bronchodilatory effects for the treatment of asthma and chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis. Leading agents in this class include Ariflo® and roflumilast. Some physicians feel that these products may have only modest benefits over theophylline. However, their roles in the treatment of asthma and COPD have yet to be determined.

The non-sedating antihistamine class may see another addition in 2004, following the completion and analysis of additional safety studies for Soltara®. In March 2002, the FDA issued a “not approvable” letter for Soltara®, making its market entry date uncertain.

BRAND NAME	GENERIC NAME	PROPOSED USE	EXPECTED RELEASE DATE				
			2003	2004	2005	2006	2007
Spiriva®	tiotropium	COPD	x				
Xolair™	omalizumab	Allergic asthma	x				
Ariflo®	cilomilast	Asthma, COPD		x			
	ciclesonide	Asthma		x			
Asmanex®	mometasone	Asthma	x				
	roflumilast	Asthma, COPD			x		
Soltara®	tecacetemizole	Allergies		x			
	TNX-901	Peanut allergies				x	

### Patent Expirations

- Flovent® 2004
- Flonase® 2004
- Allegra® 2004 (pending court ruling)
- Zyrtec® 2007
- Clarinex® 2007

## Pain/Inflammation

The marketing of biologic products for the treatment of psoriasis and psoriasis-related complications will increase disease awareness, expand treatment options and eventually transform treatment of this disease into the next multi-billion dollar market. Raptiva™ is the next new biologic agent likely to receive approval for the treatment of psoriasis. However, look for the TNF inhibitors currently on the market (e.g., Enbrel®, Remicade® and Humira™) to seek approval for the treatment of psoriasis. In 2005, the growing class of TNF Inhibitors will see the introduction of CDP-870, which has the added convenience of once-a-month subcutaneous administration. Other agents for the treatment of rheumatoid arthritis (RA) include Tenovil™, a natural anti-inflammatory and immune system regulator; and pralnacasan, an orally active small molecule drug known as an ICE inhibitor (interleukin-1b converting enzyme inhibitor), a medication that may block the formation of key cytokines involved in the inflammation process.

Two additional COX-2 inhibitors will likely compete in this multi-billion dollar market in 2004. Submission of the new drug application (NDA) for Arcoxia™ with data to support its use in ankylosing spondylitis (RA of the spine) is anticipated in mid-2003, placing its final approval sometime in 2004. The NDA for Prexige® was submitted to the FDA in 2002, but an additional clinical trial will be required to support approval, delaying final approval until at least 2004. It is unclear if these agents will offer any clinical advantages in the COX-2 inhibitor class, or only compete for a share of the market.

Antegren®, a humanized monoclonal antibody, is one of the first in a new class of alpha 4 integrin inhibitors that prevent the migration of inflammatory cells from blood vessels to sites of inflammation. Antegren® is being studied for the treatment of inflammatory diseases, including Crohn's disease and multiple sclerosis (MS).

BRAND NAME	GENERIC NAME	PROPOSED USE	EXPECTED RELEASE DATE				
			2003	2004	2005	2006	2007
Raptiva®	efalizumab	Psoriasis	x				
Prexige®	lumiracoxib	Arthritis, pain		x			
	CDP-870	RA			x		
Tenovil™	IL-10	RA			x		
Antegren®	natalizumab	MS		x			
Arcoxia™	etoricoxib	Arthritis, pain		x			
	pralnacasan	RA				x	
Humira™	adalimumab	Arthritis			x		

### Patent Expirations

- Duragesic® 2005
- OxyContin® 2007

## Cardiovascular

As the patents on several key cholesterol-lowering products begin to approach expiration, manufacturers are working to develop novel therapies for modifying cholesterol levels (raising HDL or lowering total cholesterol, LDL and triglycerides). The next entrants to the “statin” market likely will be Crestor® in late 2003, followed by pitavastatin in 2006. Avasimibe is an ACAT (acyl-coenzyme A: cholesterol acyltransferase) inhibitor that may prevent the progression of atherosclerosis as well as lower cholesterol. CP-529,414 is a cholesterol ester transfer protein (CETP) inhibitor to be used in combination with Lipitor® to elevate HDL cholesterol and lower LDL cholesterol.

Lercanidipine is a calcium blocker anticipated to compete with Norvasc® for the treatment of hypertension. Although an NDA for lercanidipine was submitted in 2001, the FDA is requiring additional clinical trials prior to granting full approval.

Exanta™ is a novel, orally-administered thrombin inhibitor for the prevention of venous thromboembolisms in orthopedic surgery. If approved, this drug is likely to compete with the low-molecular-weight heparins and Coumadin®. Dronedarone is an antiarrhythmic medication similar to amiodarone. However, a recent study of this drug was discontinued following an interim analysis showing an excess risk of death in the treatment group. An in-depth analysis of the results will be required before a new study protocol is considered.

Conivaptan is a vasopressin (V1 and V2) receptor antagonist for treatment of hyponatremia (sodium deficiency) and CHF. Fasidotril, a vasopeptidase inhibitor, is another drug being studied for the treatment of congestive heart failure (CHF) and hypertension. If development of this drug continues as planned, it will help address the increased incidence of angioedema experienced with other vasopeptidase inhibitors (e.g., Vanlev™).

BRAND NAME	GENERIC NAME	PROPOSED USE	EXPECTED RELEASE DATE				
			2003	2004	2005	2006	2007
Crestor®	rosuvastatin	Dyslipidemia	x				
Exanta™	ximelagatran	Anticoagulant		x			
	lercanidipine	Hypertension				x	
	dronedarone	Arrhythmia			x		
	pitavastatin	Dyslipidemia				x	
	avasimibe	Dyslipidemia, atherosclerosis				x	
	CP-529,414	Dyslipidemia			x		
	conivaptan	Hyponatremia, CHF			x		
	fasidotril	Hypertension, CHF					x

### Patent Expirations

- Accupril® 2003
- Monopril® 2003
- Lotensin® 2004
- Altace® 2005
- Pravachol® 2006
- Zocor® 2006
- Norvasc® 2007
- Coreg® 2007

## Women's Health

Seasonale® is likely to enter the market in 2003. This novel oral contraceptive is taken continuously for 84 days, followed by a week of placebo to allow for a menstrual period. This would decrease the number of periods from 13 to 4 per year for women taking the drug. Physicians have been prescribing monophasic oral contraceptives in a similar manner for the treatment of endometriosis, severe dysmenorrhea and migraines that worsen during the menstrual period.

With the recent FDA-recommended labeling changes for estrogen-containing hormone replacement therapies (HRT), the use of non-estrogen products for the treatment and prevention of postmenopausal osteoporosis is likely to increase. Bazedoxifene and lasofoxifene are estrogen-receptor modulators under study for the prevention of postmenopausal osteoporosis. Bonviva® likely will be the next agent introduced to the bisphosphonate market. However, a once-weekly Bonviva® formulation probably will be required to compete with the market leaders. Xyvion® is a product that possesses weak estrogenic, progestogenic and androgenic properties. Its continued development may be questionable, due to the recent FDA-requested changes to estrogen products for use as HRT.

BRAND NAME	GENERIC NAME	PROPOSED USE	EXPECTED RELEASE DATE				
			2003	2004	2005	2006	2007
Seasonale®	ethinyl estradiol/ levonorgestrel	Oral contraceptive	x				
Bonviva®	ibandronate	Osteoporosis			x		
Xyvion®	tibolone	HRT				x	
	bazedoxifene	Osteoporosis, HRT				x	
	lasofoxifene	Osteoporosis, HRT			x		

### Patent Expirations

- Nolvadex® 2003
- Ortho Tri-Cyclen® 2003
- Ortho-Novum® 7/7/7 2003
- Fosamax® 2008 (patent challenges pending)

## Anti-Infectives

Fuzeon™, approved in March 2003, is the first drug in a new class of HIV medications. Known as viral fusion inhibitors, this class of drugs prevents HIV from binding to and “fusing” with healthy T-cells, preventing the healthy cells from becoming infected. Therapy with this drug will require a subcutaneous injection twice daily, and it will be used in combination with oral medications for HIV treatment. Also in development are other drugs with mechanisms of action similar to products currently available for the treatment of HIV. They include capravirine, atazanavir and fosamprenavir. These drugs may provide incremental benefits over the current drugs, but their true place in therapy has yet to be determined.

Ketolides are a new, emerging class of antibiotic drugs. Derivatives of macrolide antibiotics (e.g., erythromycin, clarithromycin), they have been shown to be effective against some strains of macrolide-resistant bacteria. With approval expected in 2003, Ketek® likely will be the first ketolide introduced in the U.S. Other antibiotics in development include garenoxacin, a broad spectrum quinolone; and oritavancin, a glycopeptide for the treatment of gram positive infections.

FluMist™ is an intranasal flu vaccine for the prevention of respiratory influenza. As with other influenza vaccines, it will be reformulated annually to reflect the currently circulating influenza A and B viruses. Initially, it likely will be limited for use in individuals from 5 to 49 years of age. A second intranasal influenza vaccine, FluINsure™, is currently in early clinical trials.

A couple of antifungal agents are in the near-term pipeline. Ravuconazole is a broad-spectrum antifungal with activity against most of the fungi that are responsible for severe infections in patients with or without a healthy immune system (e.g., aspergillosis, mucosal candidiasis, endemic mycosis and onychomycosis). The use of posaconazole, however, likely will be limited to severe infections in individuals with a compromised immune system (e.g., aspergillosis).

BRAND NAME	GENERIC NAME	PROPOSED USE	EXPECTED RELEASE DATE				
			2003	2004	2005	2006	2007
Fuzeon™	enfuvirtide	HIV	x				
FluMist™	influenza vaccine, intranasal	Influenza vaccine	x				
FluINsure™	influenza vaccine, intranasal	Influenza vaccine				x	
Ketek®	telithromycin	Antibiotic	x				
	garenoxacin	Antibiotic		x			
	atazanavir	HIV	x				
	fosamprenavir	HIV	x				
Noxafil®	posaconazole	Antifungal		x			
	oritavancin	Antibiotic			x		
	capravirine	HIV				x	
	ravuconazole	Antifungal				x	

### Patent Expirations

- Cipro® 2003
- Diflucan® 2004
- Zithromax® 2005
- Lamisil® 2007
- Rebetal® 2003
- Biaxin® 2005
- Cefzil® 2005

## Diabetes

A new class of injectable agents for the treatment of diabetes is beginning to emerge. Modeled after natural body chemicals known as glucagon-like peptide (GLP)-1, the new agents are being studied for their roles in regulating blood glucose. The furthest in development is Symlin™, followed by exendin-4 and NN-2211.

Insulin glulisine (HMR-1964) is a rapid-acting insulin analog similar to Novolog® and Humalog®. Insulin detemir is a long-acting basal insulin that provides less day-to-day variation in insulin levels than experienced with NPH. It will compete primarily with Lantus®. The development of the inhaled insulin, Exubera™ (dry powder insulin for inhalation), has been delayed significantly from its original projected timelines due to concerns about its long-term effects on pulmonary function.

LAF-237 is a dipeptidyl peptidase (DPP) IV inhibitor for treatment of type 2 diabetes. Initial findings from a study in patients with type 2 diabetes show that it may improve glucose tolerance and insulin response to oral glucose in patients with type 2 diabetes. Glitazones in development include balaglitazone, AZ-242 and KRP-297.

Diabetes care includes not only the maintenance of blood glucose but also the management of complications associated with the disease. Ruboxistaurin (formerly known as LY333531) is a protein kinase C beta inhibitor being developed for the treatment of diabetic neuropathy, proliferative retinopathy and macular edema. Sulodexide is a heparin-type molecule for treatment of diabetic nephropathy. Pregabalin, the follow-on to Neurontin®, is also being studied for the treatment of diabetic neuropathy.

BRAND NAME	GENERIC NAME	PROPOSED USE	EXPECTED RELEASE DATE				
			2003	2004	2005	2006	2007
Symlin™	pramlintide	Glucose regulation	x				
Exubera™	inhaled insulin	Diabetes		x			
	ruboxistaurin (LY333531)	Diabetes complications				x	
	balaglitazone	Oral antidiabetic				x	
	exendin-4 (AC2993)	Glucose regulation			x		
	pregabalin	Diabetic neuropathic pain			x		
	NN-2211	Glucose regulation				x	
	insulin glulisine	Insulin analog			x		
	insulin detemir	Insulin analog	x				
	sulodexide	Diabetes complications			x		
	KRP-297	Oral antidiabetic					x
	LAF-237	Oral antidiabetic				x	

### Patent Expirations

- Glucophage® XR 2003
- Glucovance™ 2004
- Amaryl® 2005
- Actos® 2006

# NOTES