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Comprehensive information about
medications, biologics, nutrients,
and drug therapy

Formulary Information

Medication Inservices

Medications Used for Smoking Cessation

by Mandy Leonard, Pharm.D., BCPS

Introduction: It is estimated that over 40 million adults in the United States smoke cigarettes and more than 8 million of those have at least one severe illness caused by smoking.¹ Patients should be encouraged to quit smoking with the assistance of counseling and pharmacotherapies. Because it is a chronic condition, nicotine or tobacco dependence may require multiple and repeated interventions.²

Nicotine³⁻⁵: Nicotine is a ganglionic cholinergic receptor agonist, and its effects are highly dependent on dose. It causes central and peripheral nerve stimulation as well as depression. The other effects of nicotine include: respiratory stimulation, skeletal muscle relaxation, catecholamine release by adrenal medulla, peripheral vasoconstriction, and increases in blood pressure and heart rate. At lower doses, nicotine stimulates the cerebral cortex which increases alertness and cognitive function. However, at higher doses, nicotine stimulates the “reward” center in the limbic system of the brain.

As tobacco smoke, nicotine is absorbed rapidly through the lungs and one cigarette contains 10 to 25 mg of nicotine. The half-life is 1 to 2 hours, therefore, frequent and repeated administration is necessary. There is accumulation of nicotine over 6 to 9 hours with regular smoking. Nico-

tine is rapidly and extensively metabolized by the liver to approximately 20 less active metabolites. The main metabolite is cotinine, and its half-life is 15 to 20 hours.

Chronic nicotine ingestion is associated with both physical and psychological dependence. Therefore, abrupt cessation of nicotine can cause withdrawal symptoms in physically dependent smokers (e.g., anxiety, depression, difficulty concentrating, drowsiness, irritability, impatience, gastrointestinal disturbances, headache, hostility, increased appetite/weight gain, and insomnia). These symptoms may occur within 24 hours of cessation and last for days, weeks, or longer.

In 1997, the Food and Drug Administration (FDA) attempted to classify nicotine in cigarettes and smokeless tobacco as a drug and cigarettes as devices. The U.S. Supreme Court ruled in favor of the tobacco industry and decided that nicotine in cigarettes and smokeless tobacco would not be classified as a drug and cigarettes would not be classified as a device.⁴

Pharmacotherapy: The goal of nicotine replacement therapy (NRT) is to assist in smoking cessation while the patient focuses on modifying his or her behavior and coping with the psychological aspects of quitting.^{4,5} The



Table 1. Dosing Schedule for Nicotine Gum and Lozenge⁶⁻⁸

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
One piece of gum or lozenge every 1 to 2 hours	One piece of gum or lozenge every 2 to 4 hours	One piece of gum or lozenge every 4 to 8 hours

onset of action for NRT is not as rapid as that of nicotine obtained from smoking, therefore patients become less accustomed to the nearly immediate, reinforcing effects of inhaled tobacco.

The available FDA-approved smoking cessation aids include nicotine replacement products (e.g., nicotine gum, lozenge, patch, nasal spray, and inhaler), bupropion (Zyban[®]), and varenicline (Chantix[®]). Except in the presence of contraindications, nicotine replacement products and/or bupropion should be used as first-line therapy in all patients who are attempting to quit smoking to increase smoking abstinence rates.^{4,7} Second-line therapy, such as clonidine or nortriptyline, can be used if first-line therapies are not effective.^{4,7} It has yet to be determined if varenicline will be recommended as first- or second-line therapy.

Nicotine Replacement Products:

Nicotine gum and lozenge^{3,6-8}: Nicotine gum and lozenge contain nicotine bound to an ion exchange resin (nicotine polacrilex and nicotine polacrilin, respectively). Approximately 1.1 to 2.9 mg of nicotine are extracted from the 2- and 4-mg dosage forms, respectively. Long-term abstinence rates for nicotine gum and lozenge range from 30 to 80%. Both nicotine gum and lozenges are available without a prescription. For cost information regarding these products, please see Table 2.

For the gum, the dose is dependent on how much a patient smokes per day. For patients smoking ≥ 25 cigarettes per day, the starting dose is 4 mg. For patients smoking < 25 cigarettes per day, the starting dose is 2 mg. Once the dose is determined, one piece of the gum may be used every 1 to 2 hours and no more than 24 to 30 pieces per day (See Table 1 for detailed dosing schedule). Acidic beverages should be avoided while chewing the gum because of interference with buccal absorption. Additionally, eating and drinking (except for water) should be avoided 15 minutes before and after chewing. If the gum is accidentally swallowed, there is little to no absorption of nicotine. Over an extended time, nicotine gum may cause severe occlusal stress (dental) such as loosening in inlays or fillings, sticking to dentures, damage to the oral mucosa, jaw muscle fatigue, and hypersalivation. It is recommended to use the gum for no longer than 12 weeks.

For the lozenge, the dose is dependent on when the first cigarette of the day is smoked. Patients who smoke their first cigarette within 30 minutes of waking should use the 4 mg lozenge; otherwise, the 2 mg lozenge should be used. Once the dose is determined, the patient should use at least

9 lozenges per day for the first 6 weeks, but no more than 5 lozenges in 6 hours or > 20 lozenges per day. The patient should be educated to place the lozenge in the mouth and then allow it to slowly dissolve (otherwise known as the “park method”) for 20 to 30 minutes and try to minimize swallowing. The lozenge should not be chewed or swallowed. The patient should not use more than one lozenge at a time, or continuously use one lozenge after another due to increased side effects (e.g., hiccups, heartburn, and nausea). If the lozenge is allowed to dissolve completely, it delivers 25% more nicotine compared to gum. Similar to the gum, eating and drinking (except for water) should be avoided 15 minutes before and after using the lozenge. It is recommended to use the lozenge for no longer than 12 weeks.

Nicotine transdermal patch^{3,6-8}: Nicotine transdermal patches contain a multi-layered unit containing nicotine that delivers up to 24 hours of nicotine via the skin. Sixty-eight percent of nicotine released from the patch reaches the systemic circulation (i.e., the dose documented on the product [e.g., 14 mg/24 hours] is the actual amount of absorbed nicotine). Since the patch contains metal (aluminum), it needs to be removed prior to MRI. The long-term abstinence rates double with the use of nicotine patches. Nicotine patches have been available since 1991 with a prescription and since 1996 without a prescription.

Patients must completely stop smoking, chewing tobacco, or using other nicotine-containing products before using the patch. For Nicoderm[®] CQ, it is worn for 16 to 24 hours (24 hours specifically for patients who crave a cigarette upon waking). For light smokers (< 10 cigarettes per day), the patient should start with 14 mg per day for 6 weeks. For Nicotrol[®], it is worn for 16 hours (taken off at bedtime). This product should be used in patients who experience sleep disruption (See Table 3 for detailed dosing schedule). Patients should not wear more than one patch at a time and the patches should not be cut. Adverse reactions include erythema, pruritis, and burning at application site. Local skin irritation may be decreased by rotating the location of the patch.

Nicotine nasal spray^{3,6-8}: Nicotine nasal spray (Nicotrol[®] NS) delivers 0.5 mg nicotine/actuation (10 mg/mL), and there are 200 sprays or 100 doses per bottle. One mg in two sprays is delivered to the nasal mucosa and 53% reaches systemic circulation. The long-term abstinence rates double with the use of nicotine nasal spray. However, there is an *intermediate* abuse potential because of a more rapid penetration of nicotine into the central nervous

Table 2. Retail Cost Comparison of Smoking Cessation Medications⁶

Nicorette [®] Gum	F	2 mg (original): \$47 (108 pieces; \$0.44/piece)	Maximum dose of 24 pieces per day, 168 pieces = ~7 day supply Approximately \$295 for one month supply
		4 mg (original): \$52 (108 pieces; \$0.48/piece)	Maximum dose of 24 pieces per day, 168 pieces = ~7 day supply Approximately \$322 for one month supply
Commit [®] Lozenge	NF	\$45 (72 pieces; nominal pricing)	72 lozenge/9 lozenge per day = 8 day supply Approximately 4 boxes for one month supply = \$180
Nicoderm [®] CQ Patch	F	Step 1/Step 2/Step 3: \$47 (14 patches; nominal pricing)	2 boxes for one month supply = \$94 Available as clear patches \$52
Nicotrol [®] Patch	NF	Step 1/Step 2/Step 3: \$47 (14 patches; nominal pricing)	2 boxes for one month supply = \$94
Generic nicotine transdermal patch	F	\$30 (14 patches)	\$60/month
Nicotrol [®] Nasal Spray	NF	\$38 per bottle	4 bottles for one month supply = \$152 8 - 40 doses/day
Nicotrol [®] Inhaler	NF	\$121 per inhaler	Approximately one month supply (6 - 16 cartridges/day)
Zyban [®] SR	NF	\$120 (60 tablets)	One month supply
Generic bupropion SR	F	\$70 (60 tablets)	One month supply
Chantix [®]	NF	\$167.99* (11 tablets of 0.5 mg and 42 tablets of 1 mg)	One month starter pack
		\$167.99* (56 tablets of 1 mg)	One month maintenance pack

NOTE: *Average wholesale price
NF = Non-formulary; F = Formulary

system (CNS). The nasal spray has been available with a prescription since 1996.

Patients must completely stop smoking before using the nasal spray. The recommended dose is 1 to 2 doses per hour (and one dose equals two sprays, one in each nostril). Patients should use at least eight doses per day. The maximum recommended doses per hour is five with 40 doses being the maximum number of doses per day. Nicotine nasal spray should not be used for >3 months, and there is no optimal tapering strategy. Caution should be used in patients with chronic nasal disorders (e.g., rhinitis and sinusitis) and the nasal spray is not recommended in patients with reactive airway disease (e.g., asthma and COPD). Adverse reactions include headache, back pain, dyspnea, and nausea.

Nicotine inhaler^{3,6-8}: For the usual pack-per-day smoker, the hand-to-mouth motion is at least 200 times per day (or 73,000 times per year). Nicotine inhaler (Nicotrol[®] Inhaler) delivers 4 mg (10 mg/cartridge) of nicotine, but only 2 mg is systemically absorbed. The majority of nicotine from the inhaler is deposited in the mouth with only a fraction reaching lower respiratory tract. If the inhaler is used correctly, 100 puffs on the inhaler over 20 minutes is equal to 10 puffs of one cigarette over 5 minutes. The nicotine inhaler has a lower abuse potential compared to the nicotine nasal spray. The inhaler has been available with a prescription since 1997.

Patients self-titrate the initial dose, but should use at least six cartridges per day for the initial 3 to 6 weeks of therapy.

The maximum recommended dose is 16 cartridges per day. The patient should taper the doses down during the 6 to 12 weeks of therapy, and the inhaler should not be used for more than 12 weeks. Adverse reactions include local irritation, coughing, rhinitis, and dyspnea. Additionally, it may cause accelerated hypertension in patients with cardiovascular disease.

Summary of Adverse Drug Reactions and Drug Interaction with Nicotine Replacement Products^{3,4,6-8}: Patients may experience nausea and light-headedness if too much nicotine is administered. Additionally, up to 23% of patients on nicotine replacement complain of sleep disturbances. For patients that decide to use the nicotine patch, skin irritation is often a problem, and it is recommended to rotate the application site. Some patients may decide to continue to smoke while taking nicotine replacement products which increases the risk of adverse effects and causes higher peak nicotine levels compared to smoking alone. All nicotine replacement products are classified as a pregnancy-risk category D, except for nicotine gum which is classified as a pregnancy-risk category C. Pregnancy-risk category D means there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk. Pregnancy-risk category C means either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women or studies in women and animals are not available (risk versus benefit).

Cigarette smoking induces the cytochrome P450 (CYP) 1A2 isoenzyme. This is due to the polycyclic aromatic hydrocarbons (PAHs) in tobacco smoke. Therefore, doses of drugs that are substrates of the CYP 1A2 isoenzyme may need to be decreased upon smoking cessation (e.g., estradiol, diazepam, theophylline, and select opioids).

Bupropion^{3,6-8}: Bupropion is a non-nicotine medication. It inhibits neuronal uptake of dopamine and norepinephrine in the CNS, but the exact mechanism for smoking cessation is unknown. Bupropion has a half-life of 3 to

4 days, therefore, it does not reach steady-state concentrations for 5 to 8 days. It is hepatically metabolized. Bupropion (brand name Zyban[®]) is FDA-approved for smoking cessation with a prescription, but bupropion (brand name Wellbutrin[®]) is FDA-approved for the management of depression.

Patients must select a quit date because it takes bupropion 5 to 8 days to reach steady-state concentrations. The initial recommended dose is 150 mg by mouth every morning for 3 days followed by a dose increase to 150 mg by mouth twice daily. The set quit date should be within 2 weeks of beginning bupropion therapy. The duration of therapy is 7 to 12 weeks. Bupropion can be used in combination with other nicotine replacement products. Because Zyban[®] is an extended-release product, it should not be crushed. Common adverse reactions include insomnia, neuropsychiatric symptoms (e.g., delusions and hallucinations), hypertension (especially when used in combination with NRT), and dry mouth. The use of bupropion is contraindicated in patients with a history of bulimia and anorexia nervosa (due to an increased risk of seizures), seizure disorders (dose-dependent), head trauma, tumor, hepatic cirrhosis, and in patients that are on medications that decrease the seizure threshold or patients that are on a monoamine oxidase inhibitor. There are no reports of seizures in the smoking cessation trials which evaluated bupropion. Bupropion is classified as a pregnancy-risk category B which means either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester. Bupropion may be best used in patients that also have depression or who are unable to consistently use short-acting NRT. For cost information, please see Table 2.

Varenicline^{9,10}: Varenicline (Chantix[™]) is an $\alpha_4\beta_2$ nicotinic acetylcholine partial agonist. FDA-approved in May 2006, it is the newest addition to the armamentarium of smoking cessation agents. Varenicline's mechanism of action is two-fold. It binds to the $\alpha_4\beta_2$ neuronal nicotinic

Table 3. Recommended Dosing Schedule of Transdermal Nicotine for Healthy Patients⁶⁻⁸

Dose	Duration Per Strength of Patch	Entire Course of Therapy
Nicoderm CQ [®]		
21 mg/day	First 6 weeks	8 to 10 weeks
14 mg/day	Next 2 weeks	
7 mg/day	Last 2 weeks	
Nicotrol [®]		
15 mg/16 hr	First 6 weeks	10 weeks
10 mg/16 hr	Next 2 weeks	
5 mg/16 hr	Last 2 weeks	

Table 4: Varenicline Dosing⁹

Days 1-3	0.5 mg once daily
Days 4-7	0.5 mg twice daily
Day 8 - End of treatment	1 mg twice daily

acetylcholine receptors, stimulating the release of dopamine to curb nicotine cravings and withdrawal. At the same time it prevents the binding of nicotine to these receptors, interrupting the activation of the mesolimbic dopamine system. Therefore, smokers receiving varenicline therapy will not experience the usual reward associated with smoking.

Similarly to bupropion, patients must select a quit date because varenicline does not reach steady state for 4 days. Varenicline tablets should be initiated at least 1 week prior to the established quit date. Patients should receive therapy as described in Table 4. Varenicline should be administered with food and a full glass of water to decrease gastric upset. No dosing adjustments are necessary for hepatic or renal impairment. It is recommended that patients receive therapy for 12 weeks. Patients who have stopped smoking after 12 weeks of therapy should receive another 12 weeks of therapy to increase the likelihood of long-term abstinence. For those patients still smoking after 12 weeks of therapy or those who relapse, another course of varenicline therapy may be tried. Nausea is the most common side effect associated with initial varenicline use, occurring in 30% of patients. The severity of nausea may decrease with continued use. Other frequently occurring adversities include insomnia and headache. No clinically significant drug-drug interactions with varenicline have been identified, and it is not contraindicated in any patients. Varenicline is classified as a pregnancy-risk category C. Its place in smoking cessation therapy has yet to be determined. For cost information, please see Table 2.

Conclusion: Nicotine dependence is a chronic, relapsing disease that needs continual monitoring and likely repeated intervention. There are effective pharmacotherapies for nicotine dependence and should be offered to all patients with nicotine addiction. First-line therapy is NRT such as nicotine gum and transdermal patches, as well as bupropion. Second-line therapy should be offered for patients unable to use first-line medications because of contraindications or if first-line therapy is not effective. Varenicline is a new oral smoking cessation product, and its place in therapy has not yet been determined. Healthcare professionals should discuss smoking cessation options with their patients and continually play an integral role in encouraging patients to quit.

Note: For Cleveland Clinic employees to receive assistance to quit smoking, there is access to a toll-free number (1-800-QUIT-NOW) that will connect employees to a counselor and provide access to free nicotine replacement therapy. Also, employees may go to the following website www.cchs.net/wellness/WellnessFAQ.pdf for additional smoking cessation information. Furthermore, the Cleveland Clinic Employee Health Plan covers *prescription* smoking cessation products, including varenicline.

References:

1. Anon. FDA approves novel medication for smoking cessation. FDA news. May 11, 2006. <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01370.html> (Accessed August 15, 2006).
2. Flore MC, Bailey WC, Cohen SJ. Treating tobacco use and dependence, clinical practice guideline. U.S. Department of Health and Human Services. Public Health Service. June 2000. http://www.surgeongeneral.gov/tobacco/treating_tobacco_use.pdf (Accessed August 15, 2006).
3. McEvoy GK, Snow EK, Kester L, Litvak K, Miller J, Welsh OH, et al, eds. In: AHFS Drug Information. Bethesda: American Society of Health-System Pharmacists; 2006:1394-1411.
4. Doering PL. Substance-related disorders:alcohol, nicotine, and caffeine. In: DiPiro J, Tolbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: a pathophysiologic approach. 6th ed. New York: McGraw-Hill; 2005:1198-1205.
5. Taylor P. Agents acting at the neuromuscular junction and autonomic ganglia. In: Brunton LL, Lezo JS, Parker KL, eds. Goodman & Gilman's: the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill; 2006:231-3 www.crlonline.com/crlonline Accessed September 6, 2006
6. Nicotine. In: DRUGDEX[®] System [Internet database]. Greenwood Village, CO: Thomson Micromedex. Updated periodically Accessed September 6, 2006
8. Nicotine. Drug Facts and Comparisons. Drug Facts and Comparisons 4. [online]. Available from Health, Inc. Accessed September 6, 2006.
9. Varenicline package insert. Pfizer Inc, NY: Pfizer Labs; 2006 May.
10. Oncken C, Gonzales D, Nides M, Rennard S, Watsky E, Billing C, et al. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. Arch Intern Med 2006;166:1571-77.

Upcoming Topics:

Bisphosphonate-Associated Osteonecrosis of the Jaw

Gardasil[®] (Human Papillomavirus (Types 6,11,16,18) Recombinant Quadrivalent Vaccine)

New Drugs: Opana[®] and Daytrana[®]

Automatic Therapeutic Interchange Program for Pancreatic Enzymes

Pancreatic enzyme (i.e., lipase, protease, and amylase) replacement therapy is indicated for patients with: 1) deficient exocrine pancreatic secretions such as in cystic fibrosis, 2) chronic pancreatitis, 3) post-pancreatectomy, 4) ductal obstructions caused by cancer of the pancreas or common bile duct, pancreatic insufficiency, and 5) for steatorrhea of malabsorption syndrome and postgastrectomy or post-gastrointestinal surgery. It can also be used as a presumptive test for pancreatic function, especially in pancreatic insufficiency due to chronic pancreatitis.¹

Some pancreatic enzyme formulations are enteric-coated, whereas others are uncoated. Enteric-coated preparations are typically used to treat pancreatic insufficiency and steatorrhea. The enteric-coating protects the enzymes from gastric acidity thereby allowing them to reach the proximal jejunum where they aid in fat digestion.² Uncoated preparations are beneficial in treating chronic pancreatic pain syndromes. The pain is caused by high levels of cholecystikinin (CCK) over-stimulating the pancreas.² Trypsin, an activated protease enzyme, inhibits CCK-releasing factor, a peptide responsible for stimulating the release of CCK.^{2,3} Nonenteric-coated enzymes allow the release of trypsin and other proteases in the duodenum, the site where the CCK feedback mechanism is most sensitive.²

For both the enteric-coated and uncoated pancreatic enzymes, dosing is based on lipase units. In July 2006, the Cleveland Clinic Pharmacy and Therapeutics Committee approved an automatic therapeutic interchange program for all pancreatic enzymes.

1.) The preferred Formulary **enteric-coated** pancreatic enzyme will be Creon[®] Capsules (delayed-release, enteric-coated microspheres). All orders written for **enteric-coated** pancreatic enzymes will be automatically therapeutically interchanged to Creon[®] Capsules based on the lipase content.

2.) The preferred Formulary **nonenteric-coated** pancreatic enzyme will be Viokase[®] Tablets (immediate-release tablets). All orders written for **nonenteric-coated** pancreatic enzymes will be automatically therapeutically interchanged to Viokase[®] Tablets based on the lipase content.

Please contact the Drug Information Center for detailed dosing conversions of Creon[®] and Viokase[®].

References:

1. Digestive enzymes. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2006. Available from Health, Inc. Accessed April 18, 2006.
2. Forsmark CF. Chronic pancreatitis. In Feldman M, Friedman L, Sleisenger M, editors. Gastrointestinal and liver disease: pathophysiology/diagnosis/management. 7th ed. Philadelphia: Saunders; 2002. p. 943-69.
3. Pandol SJ. Pancreatic physiology and secretory testing. In Feldman M, Friedman L, Sleisenger M, editors. Gastrointestinal and liver disease: pathophysiology/diagnosis/management. 7th ed. Philadelphia: Saunders; 2002. p. 871-80.

Revised Warnings for Long-Acting Beta₂-Agonists

Long-acting beta₂-agonists (LABAs), including salmeterol (Serevent[®] Diskus[®]), the combination inhaler salmeterol/fluticasone (Advair Diskus[®]) and formoterol (Foradil[®] Aerolizer[™]), may increase the risk of asthma-related death.

LABAs are used for long-term control and prevention of asthma symptoms, for prevention of exercise-induced wheezing in adults and children, and for long-term control of wheezing in adults with chronic obstructive pulmonary disease (COPD). The new warnings for LABAs, however, are specific for patients with asthma as there is currently no data to extrapolate these concerns to other indications.

Data from a large placebo-controlled US study (Salmeterol Multicenter Asthma Research Trial [SMART]) compared the safety of salmeterol or placebo when added to usual asthma therapy. This study showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). This risk was found to be higher in African-American patients, with no increase in events among Caucasians. Serevent[®], however, is not contraindicated in the African-American population since the patients who died in the SMART study had severe asthma and a direct correlation to the use of Serevent[®] was not implicated. In August 2003, black-box warnings were added to the product labeling of all products containing salmeterol and in June 2006, a black box warning was added to the Foradil[®] Aerolizer[™] due to the potential that this increased risk of death is a class effect. The Food and Drug Administration (FDA) emphasized that the benefits of salmeterol outweigh the small risk of asthma-related deaths found in the SMART study.

In May 2006, the FDA issued a public health advisory to highlight the following recommendations:

- 1) LABAs should not be the first medication used to treat asthma, but should be added to the asthma treatment plan if other medications do not control asthma (including the use of low-or-medium dose inhaled corticosteroids).
- 2) LABAs should not be discontinued without first discussing with a healthcare professional.
- 3) LABAs do not relieve sudden wheezing; therefore, the patient should always have a short-acting bronchodilator for this indication.

At this time, per the Cleveland Clinic P&T committee, salmeterol containing products and Foradil[®] Aerolizer[™] remain on the inpatient formulary. The majority of LABA use in the hospital is due to continuation of therapy from home. Additional information including copies of the Patient and Healthcare Professional information sheets can be found at <http://www.fda.gov/cder/drug/infopage/LABA/default.htm>.

Formulary Update

The Cleveland Clinic Pharmacy and Therapeutics Committee met on Tuesday, July 11, 2006, and the following decisions were made:

Formulary Additions:

- 1.) **Oral Cephalosporins:** cefdinir (Omnicef[®]), cefixime (Suprax[®]), and cefpodoxime (Vantin[®])
- 2.) **Efavirenz 600 mg/Emtricitabine 200 mg/Tenofovir 300 mg (Atripla™):** Atripla™ is a single tablet, once-a-day therapy for the treatment of HIV.
- 3.) **Iloprost (Ventavis™):** Iloprost is an inhaled synthetic analogue of prostacyclin PGI₂ indicated for the treatment of pulmonary hypertension. Its use is *restricted* to the Pulmonary Hypertension Committee for use in patients unable to tolerate or use continuous IV prostacyclin therapy.
- 4.) **Human Papillomavirus (Types 6,11,16,18) Recombinant Quadrivalent Vaccine (Gardasil®):** Gardasil® is a vaccine indicated for girls and women aged 9-26 years for the prevention of disease caused by Human Papillomavirus types 6,11,16, and 18. Its use is *restricted* to outpatients.
- 5.) **Insulin glulisine (Apidra®):** Insulin glulisine is a rapid-acting human insulin analog. Its use is *restricted* to the Department of Endocrinology. To help distinguish it from other insulin products, please write orders as “insulin glulisine (Apidra)”.
- 6.) **Lidocaine/epinephrine/tetracaine (LET):** LET is used as a topical anesthetic. It has an improved safety profile compared to tetracaine/epinephrine/cocaine (TAC).
- 7.) **Micafungin (Mycamine™):** Micafungin is an echinocandin antifungal agent. *In vitro* activity is comparable to caspofungin with activity against *Candida* sp including *C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. kruesi*. Micafungin, like caspofungin, is also active against *Aspergillus* sp and other molds. The echinocandins have no activity against *Cryptococcus neoformans*. Micafungin appears to be well-tolerated and unlike caspofungin does not appear to interact with cyclosporine, tacrolimus, rifampin, or phenytoin. Micafungin is currently only FDA-approved for treatment of esophageal candidiasis and prophylaxis following bone marrow transplantation. However, clinical trials and reports have demonstrated efficacy in candidemia and invasive fungal infections. In addition, micafungin has been well-studied in the pediatric population. Micafungin, at the recommended dose of 150 mg daily, has substantial cost savings compared to the daily dose of caspofungin. Micafungin also appears to be comparable to caspofungin in terms of safety and efficacy. For the above reasons, micafungin has been added to the Formulary, replacing caspofungin. Its use is *restricted* to the Department of Infectious Diseases.
- 8.) **Natalizumab (Tysabri®):** Natalizumab is FDA-approved for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations. It is a humanized anti- α 4 integrin monoclonal antibody that acts as a selective adhesion-molecule inhibitor on activated lymphocytes and monocytes. Its use is *restricted* to the Department of Neurology at the Mellen Center for the outpatient treatment of MS.
- 9.) **Omega-3-acid ethyl esters (Omacor®):** Omacor® is the only FDA-approved omega-3-fatty acid product. It is indicated as an adjunct to diet to reduce triglyceride levels >500 mg/dL in adults.
- 10.) **Ramelteon (Rozerem®):** Ramelteon is a melatonin MT₁ and MT₂ receptor agonist FDA-approved for treating insomnia characterized by difficulty in falling asleep. Its use is *restricted* to the Departments of Psychiatry, Neurology, and Pulmonary Medicine.
- 11.) **Ranibizumab (Lucentis™):** Ranibizumab, an angiogenesis inhibitor, is administered as an intravitreal injection for the treatment of neovascular age-related macular degeneration. Its use is restricted to the Cole Eye Institute.
- 12.) **Rotavirus Vaccine (RotaTeq®):** Rotavirus vaccine is a live, oral pentavalent vaccine indicated for the prevention of rotavirus gastroenteritis in infants and children.
- 13.) **Zoster Vaccine (Zostavax®):** Zoster vaccine is a live vaccine indicated for the prevention of herpes zoster (shingles) in patients \geq 60 years. Its use is *restricted* to outpatients.

Formulary Deletions:

- 1.) Benzocaine and benzocaine-containing Non-Metered Dose Topical Sprays (Hurricane[®], Cetacaine[®]): Due to the potential for development of methemoglobinemia when topical benzocaine is administered incorrectly, Topex[®], a topical benzocaine metered-dose spray, will be the only topical benzocaine product on Formulary.
- 2.) Caspofungin (Cancidas[®])
- 3.) Lepirudin (Refludan[®])
- 4.) Quinupristin/dalfopristin (Synercid[®])
- 5.) Tetracaine, epinephrine, and cocaine (TAC)

Restriction Changes:

The following drug restrictions have been expanded to include:

- 1.) Bivalirudin (Angiomax[®]): The Department of Vascular Medicine for patients with heparin-induced thrombocytopenia (HIT).
- 2.) Nicardipine IV (Cardene[®]): Neurointerventional Radiology for patients with subarachnoid hemorrhage-induced vasospasm.
- 3.) Factor VIIa Recombinant (NovoSeven[®]): The Departments of Neurology and Neurosurgery for management of intracerebral hemorrhage or emergent neurosurgical intervention when INR \geq 1.4.

Therapeutic Interchange:

Beginning **Monday, August 14, 2006**, Creon[®] and Viokase[®] will be the only pancreatic enzyme preparations on Formulary. Any new orders for enteric-coated pancreatic enzyme products will be automatically therapeutically interchanged to Creon[®] and new orders for nonenteric-coated preparations will be interchanged to Viokase[®]. Product conversions will be based on lipase unit ranges. See page 6 for specific details.

Zosyn Shortage and Restriction:

There is currently a nationwide shortage of piperacillin/tazobactam (Zosyn[®]) products. The anticipated duration of the shortage is not known at this time. Therefore, Zosyn[®] will be restricted to use in Intensive Care Units and for documented infections due to Gram-negative organisms resistant to ceftazidime. The current Formulary restriction on ceftazidime will be removed. Listed below are current Formulary-approved alternatives for Zosyn[®].

Ampicillin/sulbactam (Unasyn[®]): Alternative for polymicrobial mixed aerobic and anaerobic infections which do not typically require coverage against nosocomial-acquired resistant Gram-negative organisms.

Ceftriaxone (Rocephin[®]): Recommended for use in serious community-acquired pneumonia.

Ceftazidime (Fortaz[®]): Alternative for empiric therapy or treatment of Gram-negative nosocomial infections including *Pseudomonas* infections. It may be combined with metronidazole to improve empiric anaerobic coverage or vancomycin to improve Gram-positive coverage.

**Cleveland Clinic
Department of Pharmacy/Hb-03
Drug Information Center**