Cleveland Clinic Pharmacotherapy Update
From the Department of Pharmacy

Volume XV No. IV July/August 2012

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Linagliptin: An Alternative Dipeptidyl Peptidase-4 Inhibitor

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Introduction: Diabetes mellitus affects 26 million people in the United States or about 8.3% of the population.[1] Key risk factors for type 2 diabetes include family history, excess weight, lack of regular exercise, dyslipidemia, and hypertension.[2] Uncontrolled diabetes is associated with significant morbidity including chronic kidney disease, retinopathy, neuropathy, amputations, and acute organ failure. Clinical management of patients with type 2 diabetes is intended to reach and maintain patient-specific glycemic goals. According to the American Diabetes Association (ADA), a desirable treatment target for most patients with diabetes is a hemoglobin A_{1C} (A1C) level lower than 7%, as long as the level can be accomplished safely while minimizing the risk of hypoglycemia. The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE), have a similar A1C target of 6.5% or lower for most patients.[3] First-line treatment options in type 2 diabetes involve lifestyle modifications including exercise, meal planning, and weight loss.[2,3] However, pharmacotherapy to achieve treatment goals is often required. Initial pharmacologic therapy with metformin (Glucophage®) is recommended, but may not be sufficient to achieve adequate glycemic control.[2,3] Intensification of therapy often involves an addition of an agent from a different pharmacologic class. Dipeptidyl peptidase-4 (DPP-4) inhibitors are considered a reasonable second-line pharmacologic option after metformin.[2,3] The Food and Drug Administration (FDA) approved three DPP-4 inhibitors: sitagliptin (Januvia®; Merck Company, Inc), saxagliptin (Onglyza™; Bristol–Myers Squibb Company), and linagliptin (Tradjenta™; Boehringer Ingelheim Pharmaceuticals, Inc).[4] Linagliptan, the newest DPP-4 inhibitor was approved by the FDA on May 2, 2011. The DPP-4 inhibitors are approved as an adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[5-7] Sitagliptin and saxagliptin have been evaluated for use as monotherapy or in combination with other antidiabetic agents, including metformin and thiazolidinediones when a single agent does not provide adequate control.[6,7] In addition, saxagliptin has been evaluated for use with sulfonylureas.[7] The ADA excludes DPP-4 inhibitors from the two tiers of preferred agents in their treatment algorithm due to limited data and high expense of these agents.[2] On the other hand, AACE/ACE recommends consideration of DPP-4 inhibitors for use with metformin in patients requiring dual therapy especially when experiencing hypoglycemia and/or weight gain with the other agents.[3]

Mechanism of Action: Linagliptin inhibits DPP-4, an enzyme that degrades incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[5] This activity increases the

plasma concentrations of active incretin hormones, thereby stimulating the release of insulin in a glucose-dependent manner and decreasing circulating levels of glucagon. Glucagon-like peptide-1 and GIP are involved in physiological regulation of glucose homeostasis. Both hormones increase the biosynthesis of insulin and its secretion from pancreatic beta cells in the presence of normal or elevated levels of blood glucose. Glucagon-like peptide-1 also decreases glucagon secretion from pancreatic alpha-cells, resulting in a reduction in glucose output from the liver.

Pharmacokinetics: Linagliptin has a time to peak concentration following oral administration of 1.5 hours.[5] Its bioavailability is 30%. Plasma protein binding is concentration-dependent; however, the percentage of plasma protein binding is not altered in patients with hepatic or renal dysfunction. Its elimination half-life is 12 hours and major route of elimination is enterohepatic excretion as unchanged drug.

Select Clinical Trials: Prato and colleagues conducted a trial to investigate the effect of linagliptin monotherapy on glycemic control and markers of β-cell function in patients with inadequately controlled type 2 diabetes.[8] This multicenter, randomized, double-blind trial was conducted between February 15, 2008, and May 6, 2009, at 66 sites in 11 countries. The objective was to investigate the efficacy and safety of linagliptin 5 mg versus placebo administered as monotherapy to patients with type 2 diabetes who were either treatment-naïve or who had received one oral antidiabetic drug. The inclusion criteria consisted of participants between 18 and 80 years with type 2 diabetes, body mass index (BMI) $\leq$ 40 kg/m^2, and with either an A1C of 6.5% to 9.0% and were treated with not more than one antidiabetic agent (excluding thiazolidinediones) or an A1C of 7.0% to 10.0% and were treatment naïve. Key exclusion criteria included participants who had a myocardial infarction, stroke, or transient ischemic attack within 6 months prior to randomization, impaired hepatic function, hypersensitivity to the product, treatment with more than one antidiabetic agent within 10 days, or current treatment with systemic steroids. Prior to study initiation, individuals with an A1C 6.5% to 9.0% had to undergo a 6-week washout period of previous antidiabetic medications; afterwards a 2-week placebo run-in period was initiated. Treatment-naïve patients with an A1C 7.0% to 10.0% directly entered the 2-week placebo run-in period. An A1C of 7.0% to 10.0% was required by both groups at the start of placebo run-in period. Metformin could be utilized as a rescue medication only during the randomization period in patients with a confirmed glucose level > 13.3 mmol/L after an overnight fast. Randomization was stratified by A1C < 8.5% versus $\geq$ 8.5% and by whether or not patients had previously received an oral antidiabetic drug. Following the placebo run-in period, patients were randomized to linagliptin 5 mg once daily or placebo. The primary endpoint was the change from baseline in A1C after 24 weeks. Table 1 contains study outcomes and results. A significantly smaller portion of patients receiving linagliptin required metformin rescue therapy (10.2%) compared with placebo (20.9%) with OR=0.3 (p=0.0002). Overall, 98 patients (58.7%) reported adverse events in the placebo group and 176 patients (52.4%) reported adverse events in the linagliptin group. Mean trough levels of linagliptin over time were comparable between patients with normal renal function and those with mild or moderate renal impairment. Linagliptin dose adjustments may not be required in patients with renal impairment. Both body weight and waist circumference did not differ significantly from baseline in both groups validating that linagliptin is weight neutral. The authors concluded that a clinically relevant reduction in A1C, fasting plasma glucose (FPG), and change in 2-hour postprandial glucose (2h-PPG) from baseline to week 24 were observed with linagliptin compared with placebo.

Prato and colleagues conducted a multicenter, randomized, double-blind trial between August 2008 and August 2010 at 53 sites in seven countries.[9] The objective of the trial was to examine the efficacy, safety, and tolerability of linagliptin compared with placebo in patients with type 2 diabetes who were intolerant to metformin therapy or for whom metformin was contraindicated. Participants were included if they were 18 to 80 years of age with type 2 diabetes, BMI $\leq$ 40 kg/m^2, had intolerability or contraindication to metformin, had an A1C 7.0% to 10.0% and were drug naïve or had an A1C 6.5% to 9.0% and were previously treated with one oral antidiabetic for at least 10 weeks. In order to start in the placebo run-in period patients in both groups needed an A1C of 7.5% to 11.0%. Patients naïve to diabetic treatment directly started in the 2-week placebo run-in period. Select exclusion criteria included those with a myocardial infarction, stroke, or transient ischemic attack within 6 months, impaired hepatic function, severe renal impairment, and treatment with rosiglitazone or pioglitazone, GLP-1 analogs, insulin, or antiobesity drugs in the past 3 months. Following the placebo run-in period, patients were randomized to linagliptin 5 mg once daily or placebo. The primary endpoint was the change from baseline in A1C after 18 weeks. Table 1 contains study outcomes and results. The rate of adverse events was comparable between both groups with 40.4% in the linagliptin group and 48.7% in the placebo group. The mean changes in weight and waist circumference were not significantly different between treatment groups. Additionally, the incidence of hypoglycemia was very low in the linagliptin group. The authors concluded that a clinically relevant reduction in A1C and FPG change from baseline to week 18 was associated with linagliptin which was considered well tolerated and safe.

Table 1: Efficacy Outcomes and Results[5,8,9]

Outcomes	18-Week Study		24-Week Study	
	Linagliptin 5 mg	**Placebo**	**Linagliptin 5 mg**	**Placebo**
A_{1C} (%)	n=147	n=73	n=333	n=163
Baseline (mean)	8.1	8.1	8.0	8.0
Change from baseline*	-0.4	0.1	-0.4	0.3
Difference from placebo* [95% CI]	-0.6[-0.9, -0.3]	——	-0.7[-0.9, -0.5]	——
Patients [n (%)] achieving A1C < 7%	41 (28)	11 (15)	77 (25)	17 (12)
FPG (mg/dL)	n=138	n=66	n=318	n=149
Baseline (mean)	178.4	175.6	164	166
Change from baseline*	-13.3	7.2	-8.5	14.8
Difference from placebo*[95% CI]	-20.5[-31.1, -9.9]	——	-23[-30.4, -16.3]	——
2h-PPG (mg/dL)	No data	No data	n=67	n=24
Baseline (mean)	——	——	258	244
Change from baseline*	——	——	-33.5	24.9
Difference from placebo*[95% CI]	——	——	-58.4[-82.3, 34.4]	——

*Adjusted mean A1C=Hemoglobin A1C FPG=Fasting Plasma Glucose 2h-PPG=2-Hour Postprandial Glucose

A summation of other key clinical trials including linagliptin as add-on therapy is in Table 2.

Table 2: Comparison of Linagliptin Add-On Therapy Studies [10-13]

Name	Study Design	Objective	Conclusion
Forst, 2010	MC, RCT, DB, PC, PG	To determine whether linagliptin is safe and efficacious in patients with type 2 diabetes failing to achieve glycemic control despite therapy with metformin	Treatment with the addition of linagliptin (1-, 5-, 10-mg) to metformin resulted in clinically relevant reductions in A1C and FPG compared with placebo. The 5-mg dose provided maximum glycemic control with the greatest percentage of patients achieving target A1C.
Taskinen, 2011	MC, RCT, DB, PC, PG, Phase III	To investigate efficacy and safety of linagliptin compared to placebo administered as add-on therapy to metformin in patients with inadequate glycemic control	Addition of linagliptin to metformin in patients with inadequate glycemic control showed statistically significant and clinically relevant reductions in A1C, FPG, and 2h-PPG. In addition, linagliptin was not associated with weight gain and was well tolerated.
Gomis, 2011	RCT, DB, PC, PG, Phase III	To examine efficacy, safety, and tolerability of linagliptin 5 mg once daily versus placebo as initial combination with pioglitazone 30 mg in patients with type 2 diabetes and insufficient glycemic control	Addition of linagliptin to pioglitazone produced clinically significant improvement in A1C and FPG compared with pioglitazone monotherapy. The combination therapy may be good alternative to metformin in patients with renal impairment.
Owens, 2011	MC, RCT, DB, PC, PG, Phase III	To determine efficacy, safety, and tolerability of linagliptin 5 mg versus placebo when administered in combination with a sulfonylurea in patients with type 2 diabetes and insufficient glycemic control	Addition of linagliptin in combination with metformin and sulfonylurea produced statistically significant and clinically meaningful improvements in glycemic control compared with addition of placebo. The combination therapy had a favorable safety and tolerability profile.

MC=Multicenter RCT=Randomized Controlled Trial DB=Double-blind PC=Placebo-controlled
PG=Parallel Group A1C= Hemoglobin A1C FPG=Fasting Plasma Glucose 2h-PPG=2-Hour Postprandial Glucose

Adverse Reactions: In the 24-week trial most adverse events were mild to moderate.[8] Serious adverse events occurred in ten patients (3.0%) in the linagliptin group with none of the adverse events being considered drug-related. Four patients (1.2%) reported adverse events leading to discontinuation. The most frequent adverse event was hyperglycemia, reported by five patients (1.5%) in the linagliptin group. Of the adverse events reported in more than 2% of patients, the following were more common with linagliptin than placebo: headache (2.7%), hypertension (3.6%), and back pain (2.7%). In the 18-week study two serious adverse events were reported in 2% of patients in the linagliptin group and led to discontinuation of therapy.[9] The system organ class in which adverse events were reported included: respiratory, thoracic, and mediastinal disorders in 6.6%; injury, poisoning, and procedural complications in 4.6%; and eye disorders in 2% of the linagliptin patients. Both trials had a low incidence of hypoglycemia in the linagliptin group. In addition, a clinical trial program involving linagliptin reported eight patient cases of pancreatitis compared with none in the placebo.[5] Three additional cases of pancreatitis were reported following the last administration dose.

Drug Interactions: Linagliptin has very few reported drug-drug interactions.[5] Its efficacy may be reduced when the drug is coadministered with a strong CYP3A4 or P-glycoprotein inducer such as rifampin. Rifampin therapy may decrease the level of circulating linagliptin and thus decrease its glucose-lowering effect. Also, concurrent use with other glucose-lowering agents may increase the risk of hypoglycemia.

Pregnancy and Lactation: Linagliptin is classified as pregnancy-risk category B.[5] There have not been any randomized controlled studies of linagliptin in pregnant or breastfeeding women, studies have only been performed in rats and rabbits. Therefore, the drug should only be used in pregnancy if benefit outweighs the risk. Excretion in breast milk is unknown; therefore, it should be used with caution in lactation.

Dose and Administration: The recommended dose of linagliptin is 5 mg orally once daily.[5] It may be taken with or without food. Dose adjustments are not required in renal and hepatic impairment.

Formulary Status and Cost: Linagliptin has not been added to CCHS Formulary. It is available as a 5 mg tablet. The average wholesale price (AWP) is ~$6.00 per tablet.[14] Therefore, a 30-day supply is ~$185.00. Currently, sitagliptan (Januvia®) is the only DPP-4 inhibitor on the CCHS Formulary; furthermore, a therapeutic interchange involving automatic conversion of DDP-4 inhibitors [e.g., linagliptin, saxagliptin (Onglyza™)] to sitagliptan will soon be implemented.

Conclusion: Linagliptin offers another treatment option for patients who are inadequately controlled with conventional therapy. Linagliptin has proven efficacy as both monotherapy or when added to other oral antidiabetic agents. It lowers A1C values by 0.4% to 0.7% as monotherapy or in combination with metformin, a sulfonylurea, or pioglitazone. The advantage of linagliptin over the other DPP-4 inhibitors is its lack of renal elimination, which removes the need to make dosage adjustments based on renal function. Dosage adjustments for hepatic function are also not necessary. Hypoglycemia rarely developed in patients who were treated with linagliptin and the drug has neutral effect on weight. Key differences between DPP-4 inhibitors are summarized in Table 3.

Table 3: Key Differences Between DPP-4 Inhibitors [5-7,15]

Feature	Linagliptin (Tradjenta™)	Sitagliptin (Januvia®)	Saxagliptin (Onglyza™)
FDA-approved Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 DM *		
Manufacturer	Boehringer Ingelheim	Bristol-Myers Squibb	Merck
Bioavailability	67%	87%	30%
Usual Dose	5 mg daily	100 mg daily	2.5 to 5 mg daily
Dose in Renal Impairment	No dosage adjustment	CrCl 30-50 mL/min: 50 mg daily CrCl < 30mL/min: 25 mg daily	CrCl ≤ 50mL/min: 2.5 mg daily
Hepatic Impairment	No dosage adjustment		
Metabolism	CYP3A4	CYP3A4 and CYP2C9	CYP3A4/5
Drug Interactions	Avoid rifampin	No dosage adjustments	2.5 mg daily with potent CYP3A4/5 inhibitors
Average Wholesale Price	5 mg: $6.14/tablet $184.20/30 days	100 mg: $6.62/tablet $198.50/30 days	5 mg: $6.14/tablet $184.20/30 days

FDA=Food and Drug Administration DPP-4=Dipeptidyl peptidase-4 DM=Diabetes mellitus
*On August 17, 2012 the FDA expanded the approved indication for linagliptan to include use as add-on therapy to insulin and diet and exercise to lower blood glucose in adults with type 2 diabetes.

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Formulary Update

The CCHS Medical Staff P&T Committee met on June 26, 2012, and the Cleveland Clinic Local P&T Committee met on July 9, 2012, and the following decisions were made:

Adults:
Additions to the CCHS Formulary:

Neurosciences:

1) **Factor IX complex/ Prothrombin Complex Concentrate (Profilnine®):**
   a) It is a three factor prothrombin complex concentrate (PCC) which is a mixture of non-activated vitamin K-dependent clotting factors, including factors II, IX, X, and to a lesser extent factor VII. Although the FDA-labeled indication for factor IX complex is prevention or control of bleeding in patients with factor IX deficiency (hemophilia B), the rationale for addition of factor IX complex to the Cleveland Clinic Formulary is because the American Heart Association/ American Stroke Association Guidelines for the management of spontaneous intracerebral hemorrhage provide recommendations for patients with an elevated INR due to oral anticoagulants. These Guidelines recommend the use of PCCs as a reasonable alternative to fresh frozen plasma (FFP) as a Class IIa, Level of evidence: B recommendation. Factor IX Complex is stored under refrigeration; however, should be warmed to room temperature prior to administration. The rate of intravenous administration for factor IX deficiency should not exceed 10 mL/minute due to risk of vasomotor reactions.
   b) Factor IX complex is ***restricted*** to Department of Neurology and Neurosurgery for warfarin-related life-threatening intracranial hemorrhage.
   c) **Note: Factor IX complex/ PCC is a STAT order and should be processed with the highest priority.** In addition, doses will be rounded to the nearest 100 units.
2) **Clobazam (Onfi™):**
   a) It is a 1,5-benzodiazepine FDA-approved for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older and is classified as a Schedule IV controlled substance under the Controlled Substance Act. Clinical trials have shown efficacy for clobazam compared to placebo in reduction of rates of drop seizures and total seizures from baseline in patients with Lennox-Gastaut syndrome. Clobazam was added to the Cleveland Clinic Formulary in May 2012 for continuation of home therapy in pediatric patients; however, it has now been added for use in adult patients.
   b) Clobazam use in adults is ***restricted*** to the Department of Neurology.
3) **Quetiapine extended-release (Seroquel XR®):**
   a) It is an atypical antipsychotic with multiple FDA-approved indications including schizophrenia, bipolar disorder, and major depressive disorder. The cost of extended-release quetiapine has significantly decreased since it was first marketed and therefore, it was decided to add this additional dosage form to the Cleveland Clinic Formulary. Quetiapine extended-release tablets should be swallowed whole and not crushed, chewed, or split. In addition, the extended-release tablets should be administered once daily, preferably in the evening without food or with a light meal (less than 300 calories) in order to avoid excessive drug absorption that has been observed when administered with a high-fat meal (approximately 800–1000 calories).

Critical Care/Surgery/Anesthesia:

1) **Liposomal bupivicaine (Exparel®):**
   a) It is a liposome injection of the amide local anesthetic bupivacaine, which is indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia. Bupivicaine liposome is intended for single-dose administration only and the recommended dose is based on the surgical site and the volume required to cover the area. Clinical trials have shown use of liposomal bupivicaine has increased the time to first opioid use and significantly lowered opioid intake during the postoperative period. Furthermore, this agent may offer safety advantages compared to the use of elastomeric continuous infusion pumps (e.g., ON-Q Pain Relief System). Different formulations of bupivacaine are not bioequivalent even if the milligram dosage is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to liposomal bupivicaine and vice versa. The drug can be administered undiluted or diluted up to 0.89 mg/ml (i.e., 1:14 dilution by volume) with preservative-free normal (0.9%) sterile saline for injection. In March 2012, the Institute for Safe Medication Practices (ISMP) issued an alert involving bupivicaine liposome and propofol, another medication commonly used during surgery. Unlabeled syringes of these medications have a similar white, milky appearance and could accidentally be misidentified in the operating room leading to improper administration. Bupivicaine liposome should be administered only through infiltration into the surgical site, while propofol is given intravenously.

Critical Care/Surgery/Anesthesia:

2) **Intravenous dimenhydrinate:**
   a) It is an H_1-antagonist indicated for the prevention and treatment of nausea, vomiting, or vertigo of motion sickness. Dimenhydrinate has been investigated for prophylaxis of postoperative nausea and vomiting (PONV) and as a rescue antiemetic after failure of other prophylactic antiemetics for PONV. Addition of this agent to the Formulary adds to the armamentarium of available agents for the management of nausea and vomiting, especially in light of the ongoing antiemetic drug shortages. Dimenhydrinate 50- to 100-mg can be administered intravenously (IV) or intramuscularly (IM) every 4 hours or every 4 hours as needed. When administering the drug IV, 50 mg should be diluted with 10 mL of sodium chloride 0.9% and administered over 2 minutes. For IM administration dimenhydrinate can be administered undiluted. Since dimenhydrinate can mask the symptoms of ototoxicity, caution should be used when it is administered with antibiotics that may cause ototoxicity.

3) **Tranexamic acid injection (Cyklokapron®):**
   a) It is a synthetic lysine amino acid derivative which forms a reversible complex that displaces plasminogen from fibrin resulting in inhibition of fibrinolysis. Its FDA-approved indication is in patients with hemophilia for short-term use (2 to 8 days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction. However, tranexamic acid is being added to the Formulary for an off-label indication to decrease post-operative bleeding in total joint arthroplasty (TJA). For TJA typical dosing is 10 mg/kg pre-operatively followed by a 6-10 mg/kg dose post-operatively. Doses up to 15 mg/kg/dose have been utilized. Tranexamic acid dosage reductions are recommended for patients with renal insufficiency; however, there have been no studies which recommend specific dosage adjustment for trauma-associated hemorrhage and reduction of hemorrhage in TJA. The rate of administration of tranexamic acid should not exceed 100 mg/min.

4) **Hydrocodone/acetaminophen (Norco®):**
   a) The FDA is requesting drug manufacturers to limit the strength of acetaminophen in combination prescription opioid drug products to 325 mg by January 2014. Addition of Norco® to the Formulary will start the transition towards use of acetaminophen products that contain less than or equal to 325 mg.

Internal Medicine:

1) **Novolin (R and N) insulin will be converted to Humulin (R and N) insulin.**
   a) The rationale for this Formulary conversion is due to the availability of Humulin insulin in a 3 ml vial which will reduce waste.

2) **Indomethacin suppositories (Indocin®):**
   a) It is a non-steroidal anti-inflammatory drug (NSAID) that exhibits antipyretic and analgesic properties. It is FDA-approved for the treatment of pain due to rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gouty arthritis, and bursitis/tendonitis. However, this agent is being added to the Formulary for an off-label indication due to recent evidence which supports the use of rectal indomethacin for reduction of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis in patients at high-risk for developing this condition. The dosing for rectal indomethacin suppositories for prevention of ERCP pancreatitis is a one-time 100 mg rectal dose administered post-ERCP.

Hematology and Medical Oncology:

1) ***Erwinia* Asparaginase (Erwinaze™):**
   a) It is FDA-approved as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to E. coli-derived asparaginase. Erwinaze™ contains an asparaginase specific enzyme derived from Erwinia chrysanthemi which catalyzes the deamidation of asparagine to aspartic acid and ammonia, resulting in a reduction in circulating levels of asparagine. Cytotoxicity of leukemic cells results because they are unable to synthesize asparagine and require an exogenous source for protein metabolism. The dosing for asparaginase (Erwinaze™) depends on the protocol specified. To substitute for one dose of pegaspargase: administer Erwinaze™ 25,000 units/m^2 IM three times a week on Monday/Wednesday/Friday for six doses. To substitute for a dose of native E. coli asparaginase: administer Erwinaze™ 25,000 units/m^2 IM for each dose. Asparaginase is supplied in a 10,000 unit/mL vial and each vial should be reconstituted with 1 or 2 mL of preservative-free sterile sodium chloride. The volume of reconstituted Asparaginase at a single injection site should be limited to 2 mL. Therefore, if doses are larger than 2 mL, multiple injection sites would be required.
   b) *Erwinia* Asparaginase is ***restricted*** to the Department of Hematology/Oncology for outpatient use only. It should only be prescribed to patients that have developed hypersensitivity to *E.coli*-derived asparaginase. Its use in Pediatric Hematology/Oncology patients for this indication was also previously approved.

Hematology and Medical Oncology (continued):

2) **Nilotinib (Tasigna®):**
   a) It is a tyrosine kinase inhibitor originally approved by the FDA for chronic and accelerated phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) refractory or intolerant to prior therapy. Recently, nilotinib was approved for newly diagnosed Ph+ CML in chronic phase and has been increasingly used as front-line therapy in CML patients. It is an oral chemotherapy agent that should be swallowed whole with water and taken without food approximately 12 hours apart. Patients should not consume food for at least 2 hours before the dose is taken and for at least 1 hour after. Dose adjustment may be required for hematologic (e.g., ANC and platelets) and non-hematologic toxicities (e.g., amylase, lipase, QT prolongation), and drug interactions (e.g., CYP3A4 inhibitors or inducers). A lower starting dose is recommended in patients with hepatic impairment (at baseline).
   b) Nilotinib is ***restricted*** to Staff Physicians from the Department of Hematology and Oncology for initiation of therapy; however, continuation of therapy would follow the oral chemotherapy policy (i.e., requires oral chemotherapy medications to be ordered by a staff physician only).

3) **Dasatinib (Sprycel®):**
   a) It is a tyrosine kinase inhibitor originally approved by the FDA for chronic and accelerated phase Philadelphia chromosome-positive (Ph+) CML refractory or intolerant to prior therapy. Recently, nilotinib was approved for newly diagnosed Ph+ CML in chronic phase and has been increasingly used as front line therapy in CML patients. It is an oral chemotherapy agent that can be taken once daily with or without a meal. Tablets should not be cut or crushed. Dose adjustment may be required for hematologic (e.g., ANC and platelets) and drug interactions (e.g., CYP3A4 inhibitors or inducers). Although no dosage adjustment is required for hepatic impairment, use in this patient population should be undertaken with caution.
   b) Dasatinib is ***restricted*** to Staff Physicians from the Department of Hematology and Oncology for initiation of therapy; however, continuation of therapy would follow the oral chemotherapy policy (i.e., requires oral chemotherapy medications to be ordered by a staff physician only).

4) **Pertuzumab (Perjeta™):**
   a) It is a monoclonal antibody that binds the extracellular subdomain II of the human epidermal growth factor receptor 2 protein (HER2) which ultimately results in cell growth arrest and apoptosis. Pertuzumab is indicated in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. The recommended dosage of pertuzumab is 840 mg intravenous (IV) infusion for the initial dose followed by 420 mg IV infusion every 3 weeks thereafter.
   b) Pertuzumab is ***restricted*** to the Department of Hematology/Oncology for outpatient administration only.

Did Not Add to the CCHS Formulary:

1) **Fidaxomicin (Dificid™):**
   a) It is indicated for the treatment of Clostridium difficile-associated diarrhea (CDAD) and was not added to the Formulary because it has little benefit over the current Formulary agents and also has a significantly higher cost. This agent was also denied Formulary addition in 2011.

2) **Ceftaroline (Teflaro™):**
   a) It is a "broad spectrum" intravenous cephalosporin that was not added to the Formulary because it has limited added benefit to our current Formulary agents. This agent was also denied formulary addition in 2011.

3) **Linagliptin (Tradjenta™)**

4) **Saxagliptin (Onglyza™)**

Changes in Current CCHS Formulary Restrictions:

1) **Tretinoin (ATRA; Vesanoid®)** will now be permitted to be ordered as a verbal order, which would be an exception to the oral chemotherapy policy (i.e., requires oral chemotherapy medications to be ordered by a staff physician only). Hydroxyurea is already an exception to the oral chemotherapy policy.
   a) The rationale for this change in formulary restrictions is because the American Society of Hematology now recommends an earlier start for this therapy for acute promyelocytic leukemia which may have a positive impact on early mortality.

Formulary Deletions:

1) **All strengths of quetiapine immediate-release tablets greater than 100 mg.**
   a) The rationale for deletion from the Cleveland Clinic Formulary is because higher doses (greater than 100 mg of immediate-release quetiapine) can cause increased sedation; therefore, patients need to be converted to an extended-release preparation.

Cleveland Clinic Children's Hospitals (Pediatrics):
Additions to CCHS Pediatric Formulary

1) **Silver nitrate:**
   a) Silver nitrate sticks have been re-added to Formulary for post-circumcision care.

Changes in Current CCHS Pediatric Formulary Restrictions:

1) The current restrictions for **IV acetaminophen (Ofirmev™)** will be expanded to include Staff Physicians from Pediatric Hematology/Oncology.

Frequently Asked Questions Database (FAQ)

The Frequently Asked Questions (FAQ) Database is an excellent drug information resource available to help pharmacy staff answer some common as well as unusual drug-related inquiries.

Examples of some newly added FAQs are as follows:

- Can Pentam 300 (pentamidine isethionate) for injection be used for inhalation when Nebupent for inhalation is not available?
- Can topical thrombin (Thrombin-JMI, bovine) be given via percutaneous injection to treat a pseudoaneurysm?
- Can Jehovah's Witnesses receive products that contain components of blood?
- How can copper be replenished in a copper deficient patient?

To find the answers to these and numerous other questions go to the FAQ database which is located under the Clinical Services heading on the Department of Pharmacy Homepage.

If you would like a drug information question added to the FAQ database, please contact:

Katie Stabi, Pharm.D., BCPS
Drug Information Pharmacist (REMS)
stabik@ccf.org
216-445-9348

or

Call the Drug Information Center at 216-444-6456, option #1