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Use of Inhaled Human Insulin in Patients with Diabetes Mellitus

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Introduction: Diabetes mellitus is a metabolic disease characterized by hyperglycemia and abnormal carbohydrate, fat, and protein metabolism. Diabetes has a very high prevalence worldwide. There are approximately 20.8 million (7%) people in the United States who have diabetes.[1] Diabetes results from defects in insulin secretion, sensitivity, or both. Although the exact cause remains unclear, genetics and environmental factors such as obesity and lack of exercise appear to be involved.

Diagnosis: The diagnosis of diabetes mellitus is based on one of three criteria: fasting plasma glucose (FPG), casual elevated glucose levels that occur in conjunction with symptoms, or an abnormal oral glucose tolerance test (OGTT).[2] Fasting plasma glucose is defined as the glucose level taken after no caloric intake for at least 8 hours.[2] Casual glucose levels are defined as the glucose level taken at any time of the day without regard to meals. In the OGTT test, blood glucose levels are measured 2 hours after drinking a glucose-rich beverage that contains 75 grams of glucose. This test is completed after a fast with normal FPG defined as <100 mg/dL and impaired fasting glucose (IFG) between 100 and 125 mg/dL.[2] Diabetes mellitus is defined as FPG ≥126 mg/dL, a casual plasma glucose concentration ≥200 mg/dL in the presence of symptoms, or a 2-hour OGTT value of ≥200 mg/dL.[2] The diagnosis is then confirmed by measuring any one of the three criteria on a subsequent day.[2]

Classification: Most patients with diabetes mellitus are classified as having either type 1 or type 2. Type 1 diabetes (previously known as juvenile diabetes) accounts for about 10% of all diabetes cases and is usually diagnosed in children and young adults.[2] In these patients, insulin is not produced because of immune-mediated destruction of pancreatic cells. In comparison, type 2 diabetes, which accounts for almost 90% of diabetes cases, is characterized by both insulin resistance and insufficient insulin production.[2] There are other uncommon causes of diabetes which include endocrine disorders (e.g., Cushing's syndrome), gestational diabetes mellitus, disease of the pancreas (e.g., pancreatitis) and some medications (e.g., glucocorticoids, pentamidine, and interferon alfa).[2]

Complications: It is well known that the long-term complications of diabetes include both microvascular and macrovascular complications.[3] Examples of microvascular complications include retinopathy, neuropathy, and nephropathy. Macrovascular compli-

cations include coronary heart disease, stroke, and peripheral vascular disease.[3] Good glycemic control has been shown to decrease the risk of long-term complications in both type 1 and type 2 diabetic patients.[3]

Management: The goal of treatment is to ameliorate symptoms of hyperglycemia, reduce the onset and progression of microvascular and macrovascular complications, reduce mortality, and improve quality of life. The American Diabetes Association (ADA) recommends a hemoglobin A_{1c} (HbA_{1c}) of <7%, preprandial plasma glucose of 90-130 mg/dL, and postprandial glucose <180 mg/dL.[4] These goals can be difficult to achieve in type 1 diabetics as well as in type 2 diabetics who do not respond to non-pharmacologic and oral antihyperglycemic therapy and require multiple daily insulin injections. Diabetic patients requiring exogenous insulin have traditionally received it by either subcutaneous injection with disposable needles, pen devices, or insulin pumps (i.e., portable devices that deliver rapid-acting insulin).

Type 1 and some type 2 diabetic patients require both long- and short-acting insulins to provide basal insulin coverage as well as coverage required during meal times. Over the last 2 decades, there has been an increase in the number of insulin analogues available for patients with diabetes (see Table 1).[4] Rapid-acting insulins have a faster onset of action and more predictable duration of action than regular insulin and have been used more frequently to provide meal time insulin requirements. Insulin glulisine (Apidra®) was recently approved as a rapid-acting insulin. Likewise, insulin glargine (Lantus®) and insulin detemir (Levemir®) have been introduced for basal insulin coverage since they release a constant amount of insulin over a 24-hour period.[4] There are also insulin mixtures available that contain fixed ratios of rapid- or short-acting insulin with intermediate insulin (e.g., Novolin® 70/30) to reduce the number of injections patients may need to take each day.[4] However, in an effort to mimic normal physiologic insulin response in the body, insulin mixtures are used less often resulting in more daily insulin injections. Attempts to treat diabetes by delivering insulin through non-invasive means have led to the development of a new formulation of insulin.

Inhaled Insulin: Since its first use in 1922, there have been numerous efforts towards painless administration of insulin.[7] Until now, alternative insulin administration routes have failed to deliver insulin in a reproducible and dose-dependent manner.[7] The concept of pulmonary insulin administration has become a reality with advances in technology and drug formulation.[8] Exubera®, insulin human [rDNA origin] inhalation powder (Pfizer), was approved by the Food and Drug Administration (FDA) on January 27, 2006, for the treatment of children aged 6 years or older and adult patients with type 1 or type 2 diabetes mellitus.[9] In patients with type 1 diabetes, Exubera® is used in combination with a long-acting insulin.[9] In patients with type 2 diabetes, Exubera® can be used as monotherapy or in combination with oral agents or long-acting insulin.[9] This article will review the background of inhaled insulin, its efficacy and tolerability, as well as its directions for use and place in therapy.

Pharmacology: The primary action of insulin, a polypeptide, is to regulate glucose metabolism. Insulin lowers blood glucose concentrations by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose

Table 1. Insulin and Insulin Analogues[5,6,9]

Generic	Brand Name	Manufacturer	Classification	Onset	Duration	AWP
Inhaled insulin	Exubera®NF	Pfizer	Rapid	10-20 min	6-8 h	$180.00†
Insulin lispro	Humalog®NF	Eli Lilly	Rapid	10-20 min	3-4 h	$80.35‡
Insulin aspart	Novolog®NF	Novo Nordisk	Rapid	10-20 min	3-5 h	$83.70‡
Insulin glulisine	Apridra®F	Sanofi Aventis	Rapid	10-20 min	3-4 h	$77.63‡
Insulin regular	Humulin R®NF Novolin R®F	Eli Lilly Novo Nordisk	Short	30 min	6-8 h	$54.24‡ $56.55‡
Insulin NPH	Humulin N®NF Novolin N®F	Eli Lilly Novo Nordisk	Intermediate	1-2 h	18-24 h	$54.24‡ $56.55‡
Insulin detemir	Levemir®F	Novo Nordisk	Long	3-4 h	6-23 h	$83.70‡
Insulin glargine	Lantus®F	Sanofi Aventis	Long	3-4 h	24 h	$76.98‡

F= Formulary
NF= Non-formulary
AWP= Average Wholesale Price
† = Kit (inhaler, chamber and release unit, 90- 1 mg blisters and 180- 3 mg blisters)
‡=10 mL vial

production. Insulin also inhibits lipolysis and proteolysis, and enhances protein synthesis.[4] Once inside the gastrointestinal tract, insulin is denatured. This is why insulin has only been administered by either subcutaneous (SC) injection or intravenous infusion in the past.[7]

Pharmacokinetics: The absorption of inhaled insulin depends on many factors. Each alveolus has a diameter of 0.06 to 0.2 mm and healthy adult lungs consist of about 400 million alveoli, thus forming a surface area of approximately 100 m^2.[7] In order for a drug to reach the alveoli, the inhalation system must generate the optimal aerodynamic diameter of 1-3 µm.[7] Particles larger than 5 µm linger in the oropharynx and upper airway whereas smaller particles are lost during exhalation.[7] The rate of drug absorption varies at different sites within the lung because of the variable thickness of mucosal surfaces.[7] The alveolar regions of the lungs are so densely perfused with capillaries that five liters of blood pass through the lung each minute.[7] These alveolar membranes allow the passage of proteins, such as insulin, with less degradation by proteolytic enzymes.[7]

In a Phase II randomized, cross-over study (n = 17), 6 mg of inhaled insulin demonstrated a faster onset of action than an equivalent dose of SC administered regular insulin.[10] When insulin is inhaled, the onset of glucose-lowering activity in healthy volunteers occurs within 10 to 20 minutes and is comparable to insulin lispro (see Table 1). The maximum effect on glucose-lowering occurs approximately 2 hours after inhalation.[9] The 6-hour duration of glucose-lowering activity of inhaled insulin is longer than insulin lispro and comparable to regular insulin (see Table 1).[10] Since recombinant human insulin is identical to endogenous insulin, the systemic distribution and elimination are expected to be the same.[9]

Special populations in which inhaled insulin has been studied, include pediatric, geriatric, and obese patients, those with renal or hepatic impairment, smokers, and/or those with underlying lung disease. The time to peak insulin administration for patients aged 6-11 years old is consistent with findings from the adult population. Likewise, there are no differences in the pharmacokinetics of inhaled insulin in patients older than 65 years of age.[9] For obese patients, the absorption of inhaled insulin is independent of body mass index (BMI), unlike SC administered insulin where absorption declines with increasing BMI.[9] The effect of renal or hepatic impairment on the pharmacokinetics of inhaled insulin has not been studied.

Systemic absorption of inhaled insulin varies significantly in smokers and those with underlying lung disease. The systemic insulin exposure of inhaled insulin is 2- to 5-fold higher in smokers.[9] Smokers also have a more rapid onset of action, greater maximum effect, and a greater total glucose-lowering effect (particularly during the first 2-3 hours after dosing) compared to non-smokers.[9] In contrast to the increase in insulin exposure following active smoking, when non-smokers were exposed to 2 hours of passive cigarette smoke, insulin area-under-the-cure (AUC) and maximum concentration (C_{max}) were reduced by approximately 20 and 30%, respectively.[9] In patients with unstable or poorly controlled lung disease, there are wide variations in lung function that could affect absorption and increase the risk of hypoglycemia or hyperglycemia.[9] In asthmatic patients, absorption of inhaled insulin in the absence of treatment with a bronchodilator is approximately 20% lower than absorption noted in subjects without asthma.[9] Systemic insulin concentrations are approximately 2-fold higher in patients with chronic obstructive pulmonary disease (COPD) compared to normal subjects.[9]

Select Clinical Trials: The efficacy of inhaled insulin was studied in both type 1 and type 2 diabetic patients with primary endpoints of changes in HbA_{1c}, FPG, and postprandial glucose. Type 1 diabetic patients who were stable on their current treatment were studied in two 24-week trials.[11,12] Both studies compared the regimens of preprandial inhaled insulin to preprandial regular insulin administered SC. All patients established basal insulin coverage with either once or twice daily SC intermediate- or long-acting insulin.

Quattrin and colleagues conducted an open-label, 24-week, randomized, multi-center comparative trial (n = 334) to study the efficacy and safety of preprandial inhaled insulin in combination with a single SC injection of ultralente insulin compared to a conventional SC insulin regimen.[11] The conventional SC insulin regimen consisted of NPH and regular insulin before breakfast, regular insulin before dinner, and NPH insulin either before dinner or at bedtime. The objective of the trial was to show that inhaled insulin was non-inferior to the conventional SC insulin regimen in the change in HbA_{1c} at 24 weeks with a non-inferiority margin of 0.5%. For the primary objective, inhaled insulin was non-inferior to the conventional SC insulin regimen in the mean decrease of HbA_{1c} (adjusted treatment group difference 0.16% [95% CI -0.01 to 0.32]) and had a greater reduction for both FPG (adjusted mean change difference -25.17 mg/dl [95% CI -43.39 to -6.95]) and postprandial plasma glucose (adjusted mean change difference -30.28 mg/dl [95% CI -54.58 to -5.97]). Hypoglycemic events were lower for inhaled insulin (risk ratio 0.96 [95% CI 0.93 to 0.99]). Other adverse events were comparable between the two groups. Cough, however, occurred more frequently in the inhaled insulin group and decreased as therapy continued. There were no differences in pulmonary function tests besides carbon monoxide diffusing capacity (DL_{CO}). There were increased insulin antibodies observed in the inhaled insulin group. Finally, treatment satisfaction measured by a validated questionnaire, known as the Diabetes Quality of Life and Treatment Satisfaction Questionnaire, was greater in the inhaled insulin group. The authors concluded that inhaled insulin is effective, well-tolerated, and accepted in patients with type 1 diabetes and provides glycemic control comparable to that of a conventional insulin regimen.

Skyler and colleagues conducted an open-label, 24-week, randomized, multi-center outpatient comparative trial (n = 328) to compare a basal/bolus insulin regimen involving

preprandial inhaled insulin with twice-daily SC NPH insulin to regular preprandial SC insulin with twice-daily SC NPH insulin injections.[12] The objective of the trial was to show that the inhaled insulin group was non-inferior to the SC administered insulin group in the change in HbA_{1c} at 24 weeks with a non-inferiority margin of 0.5%. Results demonstrated that inhaled insulin was non-inferior (adjusted difference -0.16% [95% CI -0.34 to 0.01]) to the SC insulin regimen in the mean decrease of HbA_{1c}. Inhaled insulin was associated with a statistically significant reduction in FPG (adjusted difference -39.5 mg/dl [95% CI -57.5 to -21.6]) compared to the SC insulin regimen group. There was no statistically significant difference between the two groups in the 2-hour postprandial concentration. Although, the overall hypoglycemia rate was lower in the inhaled insulin group (risk ratio 0.94 [95% CI 0.91 to 0.97]), the rate of severe hypoglycemia was higher in the inhaled insulin group (risk ratio 2.00 [95% CI 1.28 to 3.12]). There were no differences in pulmonary function tests except for DL_{CO}. This trial also demonstrated increased insulin antibodies in the inhaled insulin group as well as an increased incidence of cough. The authors concluded that in combination with twice-daily basal injections of NPH insulin, both inhaled and SC insulin regimens provided comparable glycemic control over 6 months in terms of HbA_{1c} reduction.

The use of inhaled insulin was also studied in patients with type 2 diabetes in comparison to SC insulin, oral thiazolidinediones, oral metformin and oral sulfonylurea or repaglinide in combination with metformin or a thiazolidinedione (see Table 2).[13-16]

Contraindications:[9] Exubera® is contraindicated in patients with hypersensitivity to any one of its excipients, smokers or those who have discontinued smoking less than 6 months prior to starting therapy, and in patients with unstable or poorly controlled lung disease since wide variations in lung function affect absorption and lead to an increased risk of hypoglycemia or hyperglycemia. If a patient starts or resumes smoking, therapy must be discontinued immediately because of increased risk of hypoglycemia, and an alternative treatment must be utilized. There are also warnings and precautions associated with the use of inhaled insulin, which are described in Table 3.

Adverse Drug Reactions:[9] The safety of inhaled insulin alone and in combination with SC insulin or oral agents, has been evaluated in approximately 2500 adult patients with type 1 or type 2 diabetes.[9] Reported non-respiratory adverse events include hypoglycemia, chest pain (4.7%), dry mouth (2.4%), and otitis media (6.5% in type 1 pediatric diabetics). Cough (4.2%) occurs more frequently with inhaled insulin and usually within seconds to minutes after insulin inhalation. The described cough is predominantly mild in severity, rarely productive, and has a decreased incidence with continued inhaled insulin use. There are also reports of mild-to-moderate dyspnea with inhaled insulin use. Patients treated with inhaled insulin demonstrated a greater decline in pulmonary function, specifically FEV_1 and DL_{CO}, than comparator-treated patients. Differences in FEV_1 and DL_{CO}, were noted within the first several weeks of treatment and did not progress over the 2-year treatment period.

Drug Interactions:[9] There are a number of medications known to affect glucose metabolism leading to insulin dose adjustment and monitoring. These drug interactions are similar to those noted with injectable insulin, with one notable difference. Bronchodilators and other inhaled products may alter the absorption of inhaled human insulin. Therefore, consistent timing of bronchodilator administration relative to inhaled insulin administration, close monitoring of blood glucose concentrations, and dose titration as appropriate are recommended by the manufacturer.

Pregnancy and Lactation:[9] Inhaled insulin absorption in pregnant patients with gestational or pre-gestational type 2 diabetes is consistent with that of non-pregnant patients with type 2 diabetes. Since animal reproduction studies have not been conducted with inhaled insulin, it is unknown whether inhaled insulin can cause fetal harm when administered to a pregnant woman. Exubera® is classified as a pregnancy-risk category C, defined as either animal studies have revealed adverse effects on the fetus or there are no controlled studies in pregnant women, which is why it should be given only if the potential benefit justifies the potential risk to the fetus. However, SC insulin is classified as a pregnancy-risk category B and is the drug of choice for the control of diabetes mellitus in pregnancy.[17] Human insulin is excreted in breast milk and caution should be taken when insulin is administered to a nursing woman. However, since the gastrointestinal tract destroys insulin, systemic absorption of the lactating infant is not expected. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both.

Dose and Administration:[7,9] The dry-powder formulation of insulin described in this review is a mix of human insulin (rDNA origin), mannitol (stabilizing agent), glycine, and sodium citrate. The insulin powder is available in single-dose blister packs of 1- or 3-mg. Directions for use must be adequately explained to patients initiated on inhaled insulin to reduce administration errors. The insulin blisters are placed into a slot on the inhaler device. Once pierced, the contents are dispersed by compressed air into a visible aerosol cloud, which is captured in a holding chamber. The patient inhales from this chamber at the beginning of a deep, slow breath. If the insulin dose is not exactly 1- or 3-mg, the patient will need to inhale the contents of multiple blisters. Bioavailability does not appear to be enhanced by holding the breath at the end of inspiration.[7]

As with other insulins designed for mealtime use, the dosage of inhaled insulin must be titrated to the needs of individual patients. Any changes to the insulin dose should be made cautiously and under medical supervision. Because of the rapid onset of action, the dose should be given within 10 minutes before a meal to prevent hypoglycemia. In patients with type 2 diabetes, concomitant oral antihyperglycemic therapy

Table 2. Select Trials of Preprandial Inhaled Insulin in Type 2 Diabetes

Author (year), number of patients	Treatment Groups	Adjusted Difference in HbA_{1c}	Adjusted Difference in FPG	% of Patients with HbA_{1c} <7%	Hypoglycemia Events	Authors' Conclusions
Hollander[13] (2004) n = 299 24-week	Preprandial inhaled insulin plus bedtime dose of ultralente vs. at least 2 injections of SC insulin (mixed regular/NPH insulin)	HbA_{1c} decreased similarly in inhaled (-0.7%) and SC (-0.6%) insulin groups. Adjusted treatment group difference -0.07% [95% CI -0.32 to 0.17]	FPG decreased greater in inhaled (-20 mg/dl) vs. SC (-9 mg/dl) insulin group. Adjusted treatment group difference -15.9 mg/dl [95% CI -26.6 to -5.2]	Higher % of patients in inhaled (46.9%) vs. SC (31.7%) insulin group, odds ratio 2.27 [95% CI 1.24 to 4.14]	Less events/subject month in inhaled (1.4) vs. SC (1.6) insulin group, risk ratio 0.89 [95% CI 0.82 to 0.97]	Inhaled insulin provides glycemic control comparable to a conventional SC regimen and appears to be effective, well tolerated, and well accepted in patients with type 2 diabetes.
Defronzo[14] (2005) n = 145 12-week	Preprandial inhaled insulin vs. rosiglitazone	HbA_{1c} decrease was greater in inhaled insulin (-2.3%) vs. rosiglitazone (-1.4%) group. Adjusted treatment group difference -0.89% [95% CI -1.23 to -0.55]	FPG decreased similarly in inhaled insulin (-64 mg/dl) vs. rosiglitazone (-56 mg/dl) group. Adjusted treatment group difference -4 mg/dl [95% CI -18 to 9]	Higher % of patients in inhaled insulin (44%) vs. rosiglitazone (18%) group, odds ratio 4.43 [95% CI 1.94 to 10.12]	More events/subject month in inhaled insulin (0.7) vs. rosiglitazone (0.05) group, risk ratio 14.72 [95% CI 7.51 to 28.83]	Inhaled insulin could be an effective therapy for patients with type 2 diabetes early in the course of disease.
Barnett[15] (2006) n = 427 24-week	Preprandial inhaled insulin and metformin vs. glibenclamide and metformin	HbA_{1c} decreased similarly in inhaled insulin (-2.03%) vs. glibenclamide (-1.88%) group. Adjusted treatment group difference -0.17% [95% CI -0.34 to 0.01]	No difference in FPG between groups, actual differences not reported. Adjusted treatment group difference 0.98 mmol/l [95% CI -7.13 to 9.1]	No difference in % of patients in inhaled insulin (37.2%) vs. glibenclamide (31.1%) group, odds ratio 1.32 [95% CI 0.87 to 2]	More events/subject month in inhaled insulin (0.18) vs. glibenclamide (0.08) group, risk ratio 2.24 [95% CI 1.58 to 3.16]	In patients with type 2 diabetes poorly controlled on metformin, addition of inhaled insulin or glibenclamide was similarly effective in improving glycemic control, and both were well tolerated.
Rosenstock[16] (2005) n = 309 12-week	Three arms: 1) Preprandial inhaled insulin plus existing stable regimen of 2 oral agents 2) Preprandial inhaled insulin monotherapy 3) Existing stable regimen of 2 oral agents *Oral agents = a sulfonylurea or repaglinide and a thiazolidinedione or metformin	HbA_{1c} decrease was greater in inhaled insulin plus 2 oral agents (-1.9%) vs. 2 oral agents (-0.2%). Adjusted treatment group difference -1.67 % [95% CI -1.9 to -1.44] HbA_{1c} decrease was greater in inhaled insulin monotherapy (-1.4%) vs. 2 oral agents (-0.2%) Adjusted treatment group difference -1.18% [95% CI -1.41 to -0.95]	FPG decrease was greater in inhaled insulin plus 2 oral agents (-53 mg/dl) vs. 2 oral agents (1 mg/dl) group. Adjusted treatment group difference -53 mg/dl [95% CI -66 to -41] FPG decrease greater in inhaled insulin monotherapy (-23 mg/dl) vs. 2 oral agents (1 mg/dl) group Adjusted treatment group difference -24 mg/dl [95% CI -36 to -11]	Higher % of patients in inhaled insulin plus 2 oral agents (32%) vs. 2 oral agents, odds ratio 44.7 [95% CI 6 to 335] Higher % of patients in inhaled insulin monotherapy (17%) vs. 2 oral agents (1%) group, odds ratio 19 [95% CI 2.5 to 145.8]	More events/subject month in inhaled insulin plus 2 oral agents (1.7) vs. 2 oral agents (0.1), risk ratio 32 [95% CI 19 to 54] More events/ subject month in inhaled insulin monotherapy (1.3) vs. 2 oral agents (0.1), risk ratio 24 [95% CI 14 to 42]	Inhaled insulin improved overall glycemic control and HbA_{1c} when added to or substituted for dual oral agent therapy with an insulin secretagogue or sensitizer.

RCT = Randomized Controlled Trial; SC = Subcutaneous

*All trials in Table 2 were open-label, parallel group, multi-center, non-inferiority randomized controlled trials.

Table 3. Warnings and Precautions for Inhaled Insulin Use[9]

Allergic Reactions	Include rash, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating
Hypoglycemia	Caution in patients with long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control
Pulmonary Function	Assess prior to initiating therapy, use not recommended in patients with baseline FEV_1 or DL_{CO} < 70%
Acute Illness	Insulin requirements may be altered
Bronchospasm	Discontinue therapy and seek medical attention
Renal/Hepatic Impairment	Insulin dose may need to be reduced
Insulin Antibodies	Clinical consequences unknown

may need to be adjusted after initiating inhaled insulin therapy. Finally, adjustment of insulin dosage may be necessary for changes in physical activity or meal plans.

An FDA-approved medication guide must be distributed when dispensing an outpatient prescription for Exubera® and can be found at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. The Exubera® Release Unit in the inhaler should be changed every 2 weeks, which requires manual dexterity. The Exubera® inhaler must be cleaned weekly and allowed to air dry, since moisture in the chamber absorbs the insulin powder. The inhaler may be used for 1 year. There are two release units packaged with every refill kit.

The initial preprandial dose is 0.05 mg/kg, rounded down to the nearest whole number based on the findings of clinical trials in which patients consumed three meals per day. If the patient is being switched from regular SC insulin, dose conversions should be made based on Table 4. The foil blisters should be combined so that the smallest possible number of blisters are used for each dose. For example, if a patient has been taking 10 units of SC regular insulin and is switched to inhaled insulin, the units should be rounded to 11 units. Therefore, the patient would begin inhaled insulin treatment with a total of 4 mg which is equivalent to one 3 mg and one 1 mg blister. The patient would then have to closely self-monitor blood glucose.

Although there are no specific guidelines on how to round SC insulin units to equal inhaled insulin doses, inhaled insulin doses should match as closely as possible to the original SC dose. It should be noted that three consecutive 1 mg doses of inhaled insulin provide more insulin than a 3 mg blister and should therefore not be substituted for the 3 mg dose. This information has been addressed in an Institutes of Safe Medication Practices (ISMP) Safety Alert and can be reviewed at http://www.ismp.org/Newsletters/acutecare/articles/A4Q06Action.asp.

Monitoring[9]: Before initiating therapy with inhaled insulin, all patients should have spirometry performed as well as an assessment of DL_{CO}. The monitoring of lung function is also recommended after the first 6 months of therapy, and annually thereafter, even in the absence of pulmonary symptoms. The use of inhaled insulin with an FEV_1 or DL_{CO} less than 70% of normal is not recommended. In patients who have a decline of ≥20% in FEV_1 from baseline, pulmonary function tests should be repeated. If the ≥20% decline from baseline FEV_1 is confirmed, therapy should be discontinued. The presence of pulmonary symptoms and lesser declines in pulmonary function may require more frequent monitoring of pulmonary function and consideration of discontinuation of inhaled insulin. During respiratory illness, close monitoring of glucose levels are required and the inhaled insulin dose may need to be adjusted. Patients should also be made aware that the use of bronchodilators may alter inhaled insulin absorption.

Cost/Formulary Status: The cost of inhaled insulin is significantly higher than SC administered insulin (see Table 1).[6] However, the benefit of treatment satisfaction and the potential positive impact on treatment adherence may offset the additional cost of inhaled insulin.[19] Since patient satisfaction declines in patients with diabetes who require multiple daily SC injections, resulting in decreased patient compliance, any non-invasive therapy that delivers the same therapeutic benefit is likely to be of considerable interest from a patient acceptability and compliance point of view. This is true regardless if the drug is more costly, as shown by a Canadian study.[19] Inhaled insulin is not on the inpatient Formulary at Cleveland Clinic.

Summary: The benefit of an intensive insulin regimen has been demonstrated in the Diabetes Control and Complications Trial. Despite these advantages, there are barriers to insulin use because of decreased patient acceptance as a result of multiple daily injections. Inhaled insulin has a unique place in the treatment of diabetes to achieve glycemic control and thereby reduce the risk and slow the progression of long-term complications in patients who are averse to insulin injections and have good lung function. Traditionally, patients have used intermediate- to long-acting insulin to provide basal insulin as well as short-acting insulin at mealtime when physiologic requirements of insulin were increased. Patients now have an inhaled

Table 4. Approximate Equivalent Doses of Inhaled Human Insulin (Exubera®) and Subcutaneous (SC) Regular Human Insulin[9]

Approximate equivalent dose of SC regular insulin (units)	Dose of inhaled insulin (mg)	Number of 1 mg blisters of inhaled insulin	Number of 3 mg blisters of inhaled insulin
3	1	1	
6	2	2	
8	3		1
11	4	1	1
14	5	2	1
16	6		2

Adapted from package labeling

insulin formulation to use for mealtime insulin requirements. The disadvantages of using inhaled insulin include variations in absorption that are age-related or due to respiratory tract infections and smoking, as well as cost. Patients should be made aware that inhaled insulin is not a comprehensive replacement of SC insulin since there is still a need for daily injections of basal insulin requirements, but it will certainly reduce the number of insulin injections required each day.

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Formulary Additions

The Cleveland Clinic Pharmacy and Therapeutics Committee met on Tuesday, January 9, 2007, and the following decisions were made:

1. **Carvedilol CR (Coreg CR™):** Carvedilol 10-, 20-, 40-, and 80-mg extended-release capsules are intended for once daily administration. Please refer to product labeling for dose conversions between immediate-release and extended-release carvedilol formulations. These capsules will become commercially available by the end of the first quarter of 2007 and will be stocked in addition to immediate-release carvedilol tablets.

2. **Conivaptan (Vaprisol®):** Conivaptan is the first in a new class of diuretics that block antidiuretic hormone or vasopressin receptors V_{1A} and V_2. By binding to the V_{1A} receptor it blocks the effect of vasopressin, whereas its aquaretic effects are due to its binding at the V_2 receptor. It is indicated for the treatment of euvolemic hyponatremia in hospitalized patients. Conivaptan use is ***restricted*** as follows:

- Restricted to intensive care unit patients with:
  - Severe hyponatremia <120 mmol/L and
  - Symptoms attributed to hyponatremia not responsive to standard treatment
- Patients must fail standard therapies for treating hyponatremia:
  - Adequate free water restriction in appropriate patients
  - Furosemide diuresis in appropriate patients
  - Saline infusion in appropriate patients
  - Demeclocycline in appropriate patients

A loading dose of 20 mg should be administered intravenously over 30 minutes. The maintenance dose is a continuous infusion of 20 mg administered over 24 hours for 4 days maximum. The continuous infusion may be titrated to 40 mg daily if the serum sodium is not increasing as desired. However, the total duration of the infusion should not exceed 4 days. It is recommended that conivaptan be infused via a large vein and that the infusion site be changed every 24 hours to decrease the risk of vascular irritation. Because a rapid rise in serum sodium (i.e., >12 mEq/L per day) may result in negative sequelae, serum sodium, volume, and neurologic status should be monitored frequently during treatment. In addition, patients should be monitored for infusion site reactions including phlebitis, inflammation, and thrombosis. Conivaptan is available as 5 mg/mL (4 mL) vials.

3. **Decitabine (Dacogen™):** Decitabine, an antimetabolite (pyrimidine), is FDA-approved for the treatment of patients with myelodysplastic syndrome (MDS) including previously treated and untreated de novo and secondary MDS of all French-American-British (FAB) subtypes, Intermediate-1, Intermediate-2, and high-risk International Prognostic Scoring System Groups. Decitabine use is ***restricted*** to the Department of Hematology and Medical Oncology for both outpatient and inpatient administration.

4. **Insulin detemir (Levemir®):** Insulin detemir is a long-acting insulin analogue indicated for once or twice daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal insulin control for hyperglycemia. Its use is ***restricted*** to patients who currently receive insulin detemir at home or initiation of therapy in inpatients as prescribed by Endocrinology. To help distinguish this insulin from other insulin products, please write orders as "insulin detemir (Levemir®)".

5. **Panitumumab (Vectibix™):** The monoclonal antibody, panitumumab, is FDA-approved for the treatment of epidermal growth factor receptor-expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens. Panitumumab use is ***restricted*** to the Department of Hematology and Medical Oncology for **outpatient** use only.

6. **Rifaximin (Xifaxan™):** Rifaximin is FDA-approved for the treatment of travelers' diarrhea; however, there are data for using it to treat hepatic encephalopathy. The most commonly used dose for hepatic encephalopathy is 400 mg orally three times daily; however, doses ranging from 600 mg to 2400 mg/day have been studied. Rifaximin is available as 200 mg tablets and its use is ***restricted*** to patients with hepatic encephalopathy who have failed first-line therapies, such as lactulose or neomycin.

7. **Sitagliptin (Januvia™):** Sitagliptin is in a new class of agents known as dipeptidyl peptidase-IV inhibitors. It is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. It can be used alone or in combination with metformin or a peroxisome proliferator-activated receptor gamma agonist (e.g., thiazolidinediones). Sitagliptan is available as 25-, 50-, and 100-mg tablets. The recommended dose is 100 mg orally once daily with dosage adjustments recommended in patients with renal impairment.

Restriction Changes:

1. The recombinant Factor VIIa (NovoSeven®) restriction has been changed to include Departments of Hematology/Medical Oncology, Vascular Medicine, Neurology, Neurosurgery, and Medical Staff from the Liver Transplant Team for the following hepatology patients:

- Fulminant Hepatic Failure: to permit insertion of an intracranial pressure (ICP) monitor in patients with coagulopathy who are either unresponsive to conventional measures or unable to tolerate the volume load that would result from administration of multiple units of fresh frozen plasma. The decision to administer should be determined by a multidisciplinary team including the Liver Transplant Surgeon, Critical Care Staff, Neurosurgery Staff, and Staff Hepatologist.
- "Rescue Therapy" During Liver Transplantation: in patients with life-threatening bleeding and severe coagulopathy unresponsive to conventional measures and exhaustive surgical control attempts. Due to the risk of thromboembolic phenomena, the decision to administer should be determined by both the Liver Transplant Surgeon and Staff Anesthesiologist.

The initial dose is 80 mcg/kg (based on actual body weight or adjusted body weight if patient is 25% over their ideal body weight) rounded to the nearest vial size and given as an IV push. The dose may be repeated once after 2 hours if bleeding continues despite adequate amounts of blood products as determined by the Liver Transplant Surgeon/Staff Anesthesiologist.

2. The iron sucrose (Venofer®) restriction has been changed to include the Department of Adult Nephrology for **outpatient** use only and Pediatric Nephrology.

Formulary Deletions:

1. Injectable ziprasidone (Geodon®)

Automatic Therapeutic Interchanges:

1. **5HT3 Receptor Antagonists for Chemotherapy Induced Nausea and Vomiting (CINV) and Postoperative Nausea and Vomiting (PONV) Automatic Therapeutic Interchange:**

a. Beginning Tuesday, January 30th, 2007, all **inpatient CINV** orders for granisetron (Kytril®) and dolasetron (Anzemet®) will be automatically converted to generic ondansetron.

Dose Conversions of Dolasetron IV and Granisetron IV to Generic Ondansetron IV for CINV (Adults)

Dolasetron 100 mg IV daily = Ondansetron 8 mg IV daily
Granisetron 1 mg IV daily = Ondansetron 8 mg IV daily
For inpatient palonosetron orders for CINV, treat these orders as non-formulary (i.e., no automatic interchange to ondansetron). Contact physician and state that palonosetron is non-formulary for inpatients and ask if they will consider changing the order to ondansetron 8 mg IV daily.

Dose Conversions of Dolasetron PO and Granisetron PO to Ondansetron PO for CINV (Adults)

Dolasetron 100 mg PO daily = Ondansetron 16 mg PO daily
Granisetron 2 mg PO daily= Ondansetron 16 mg PO daily

b. Beginning Tuesday, January 30th, 2007, all **inpatient and outpatient PONV** orders for granisetron (Kytril®), dolasetron (Anzemet®), and palonosetron (Aloxi®) will be automatically converted to generic ondansetron.

Dose Conversions of Dolasetron IV to Ondansetron IV for PONV (Adults)

Dolasetron 12.5 mg IV x 1 dose = Ondansetron 4 mg IV x 1 dose
Dolasetron 12.5 mg IV Q 8 hours prn x 24 hours = Ondansetron 4 mg IV Q 6 hours prn x 24 hours

Dose Conversions of Dolasetron PO to Ondansetron PO for PONV (Adults)

Dolasetron 50 mg PO x 1 dose = Ondansetron 8 mg PO x 1 dose
Dolasetron 100 mg PO (120 minutes prior to induction of anesthesia) x 1 dose = Ondansetron 16 mg PO (60 minutes prior to induction of anesthesia) x 1 dose

2. **Rapid-Acting Insulin Analogue Automatic Therapeutic Interchange:**
Within the next month or so, Cleveland Clinic will transition to a single rapid-acting insulin analogue. All orders written for insulin aspart (Novolog®) or insulin lispro (Humalog®) will be automatically converted to insulin glulisine (Apidra®). Additional communications regarding this interchange will be sent in the near future.

For more detailed information on the above medications, please consult the Formulary on the Intranet (under Clinical Resources/ Drug Information), specifically under Lexi-Drugs Online. Furthermore, please call the Drug Information Center at 4-6456, option #1 if you have any questions.

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