CLINICAL THERAPEUTICS

Inhaled Insulin for Diabetes Mellitus

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.*

A 52-year-old man with an 8-year history of type 2 diabetes mellitus visits his primary care provider for advice. His glucometer readings at home have been high despite treatment with a sulfonylurea, a thiazolidinedione, and metformin at maximal doses. He has never smoked. His glycated hemoglobin value is 8.6% and his fasting blood glucose concentration ranges between 170 and 220 mg per deciliter (9.4 and 12.2 mmol per liter). His blood pressure, weight, and lipid profile are within recommended target ranges. The patient and his physician discuss therapeutic options and agree that insulin treatment should be initiated. The physician wonders whether the patient might benefit from inhaled insulin and refers him to an endocrinologist for evaluation.

THE CLINICAL PROBLEM

Diabetes mellitus, a major cause of illness and death across the globe, is responsible for a growing proportion of national health care expenditures. Insulin treatment is necessary for a substantial minority of patients with diabetes; more than 5 million Americans take insulin injections every day.[1-4] A wide range of subcutaneous insulins are available, many administered with penlike delivery devices and ultrafine needles that enhance the comfort and convenience of insulin treatment.[5] However, surveys indicate substantial resistance to insulin therapy on the part of both patients with type 2 diabetes who are not taking insulin and clinicians who care for such patients; the reasons for this resistance include anticipated pain, inconvenience, fear of hypoglycemia, and concern about weight gain.[6-8] True insulin and needle phobias are uncommon, although many patients appear to avoid insulin injections and blood glucose testing because of anxiety.[6,9-11] The youngest and oldest patients are least likely to accept injectable therapy and thus pose the greatest challenge for physicians who want to initiate insulin treatment.[12] Although resistance can be mitigated through education, efforts to develop oral, nasal, and inhaled formulations of insulin have been driven by the preference of patients to avoid subcutaneous injections.[13]

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Insulin is lifesaving for patients with type 1 diabetes, a disease characterized by beta-cell failure and insulin deficiency. Type 2 diabetes, by contrast, is characterized by defects in both insulin secretion and insulin action, with insulin deficiency usually emerging later in the course of the disease. Insulin supplementation is often required to attain good glycemic control in type 2 diabetes and is typically initiated if the glycated hemoglobin level is not in the target range despite treatment with a combination of oral hypoglycemic agents.[14]

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N Engl J Med 2007;356:497-502.

Most proteins and peptides used for systemic therapeutic purposes, including insulin, have high molecular weights and are hydrophilic; as a result, the only suitable means of administration has been injection.[15] However, inhalation devices can now facilitate delivery of drugs to the lungs. Since the lung is a large microvascular organ, molecules that are formulated to reach the alveoli can gain access to the systemic circulation.[15,16] Effective distribution in the lung requires particles that have an aerodynamic diameter between 1 and 5 μm.[15,16]

Many inhaled medications do not require a high degree of precision in dosing, and portable devices for inhaled drug delivery may be characterized by considerable dose-to-dose variation because of differences in inhalational flow rates. These devices are unsuitable for the administration of drugs such as insulin, for which dose consistency is critical.[17] The development of suitable inhalation devices has therefore been a limiting factor in the production of a reliable, clinically useful form of inhaled insulin.

So far, the only device for insulin inhalation that has been approved by the Food and Drug Administration (FDA) is an inhaler that delivers a dry-powder formulation of human insulin produced by means of recombinant DNA technology (Exubera, Pfizer). After oral inhalation of a single dose of human insulin by means of this device, approximately 40% of the dose reaches the deep lung, and 10% of the total dose is bioavailable.[18-20] The amount of drug that is delivered to the oropharynx or swallowed is unlikely to have a clinical effect.[20]

The interval between the administration of insulin and the onset of glucose-lowering activity is shorter with inhaled insulin (10 to 20 minutes) than with subcutaneously administered soluble (regular) human insulin and is similar to the interval with subcutaneously administered rapid-acting insulin analogues such as aspart, glulisine, and lispro. These pharmacokinetic features make inhaled insulin a suitable agent for preprandial administration. Its duration of action is between that of the rapidly acting insulin analogues and that of regular human insulin.[20-22]

CLINICAL EVIDENCE

Inhaled insulin has been compared with subcutaneous insulin regimens in patients with type 1 diabetes and in those with type 2 disease and has been compared with oral hypoglycemic agents in patients with type 2 diabetes.[23] All these trials were open label; most lasted for less than 6 months, and more than 90% of the participants were white.[23,24]

Among patients with type 1 or type 2 diabetes who received either a combination of neutral protamine Hagedorn (NPH) and regular insulin two to three times daily or a combination of ultralente each night and inhaled insulin before each meal, the glycated hemoglobin level at 6 months did not differ significantly between the two treatment groups. Patients who received ultralente and inhaled insulin had slightly lower rates of hypoglycemia.[25,26]

Adding thrice-daily inhaled insulin to existing oral therapy is generally more effective over a 12-to-24-week period than adding a second oral hypoglycemic drug taken once or twice a day.[27-29] However, as compared with oral agents for diabetes, inhaled insulin is consistently associated with a significantly higher incidence of hypoglycemic events.[23,27-30]

In clinical trials, patients have been generally more satisfied with inhaled insulin than with subcutaneous insulin.[25,26,31,32] Whether this outcome will be borne out in clinical practice remains to be determined.

CLINICAL USE

The FDA and the European Medicines Agency have both approved the Exubera inhalation delivery system for the preprandial treatment of patients with type 1 or 2 diabetes.[18,33] Therefore, most of the available information regarding the use of inhaled insulin is based on studies of this agent. Several other manufacturers have preparations of inhaled insulin that are being evaluated in clinical trials but have not yet been approved.

Because of its rapid onset of activity, inhaled insulin is suitable for preprandial but not for basal use. Patients with diabetes that is suboptimally controlled with the use of oral agents alone can usually be successfully treated at the outset by adding a single subcutaneous dose of either NPH or glargine insulin that is given before bedtime and titrated to a target fasting glucose level of approximately 100 mg per deciliter (5.5 mmol per liter).[34] Patients who comply with such an ap-

proach and whose glycated hemoglobin levels remain above target levels while they are receiving a basal insulin benefit from additional preprandial insulin therapy. Preprandial insulins such as inhaled insulin are therefore most suitable for patients with glycated hemoglobin levels that remain elevated after fasting glucose levels have been controlled with a basal insulin.

Inhaled insulin therapy may be especially useful for patients with a true needle phobia and those with extensive cutaneous lipodystrophy at injection sites, although the incidence of the latter problem is declining.[6] Inhaled insulin is not approved for use in pregnant women, children, or adolescents.

Smoking is a contraindication to the use of inhaled insulin; active smoking significantly increases the rate and extent of insulin absorption.[35,36] In contrast, passive exposure to tobacco smoke in nonsmokers decreases the rate and extent of insulin absorption.[37] Clinicians should therefore exercise caution if they are prescribing inhaled insulin for patients who work or live in a smoky environment.

The use of inhaled insulin in patients with underlying lung disease such as asthma or chronic obstructive pulmonary disease is not recommended, since the absorption of insulin in these patients can be unpredictable, particularly when they are also using an inhaled bronchodilator.[37,38] A simple upper respiratory tract infection may be less problematic: according to the manufacturer of Exubera, an experimental rhinovirus infection did not change the absorption of inhaled insulin.[37] There are no data regarding the effect of more severe respiratory tract infections, such as pneumonia, on the absorption of inhaled insulin. Nevertheless, it is prudent for patients initiating treatment with inhaled insulin to be trained in the use and receive a supply of subcutaneous insulin for situations in which pulmonary absorption might not be reliable.

All candidates for inhaled insulin therapy should be taught how to check their glucose level before meals. They should also undergo spirometry, and the drug should not be used if the forced expiratory volume in 1 second (FEV_1) is below 70% of the predicted value. Measurement of the diffusing capacity for carbon monoxide is not mandatory but can provide a useful baseline for monitoring changes in pulmonary function over time.

With the Exubera inhalational device, the actuation of the dose and the inhalation are separated into two steps (see the video in the Supplementary Appendix, available with the full text of this article at www.nejm.org). When a dose of insulin is required, the patient extends the chamber and places a single blister of powdered insulin into a slot in the front of the device (Fig. 1). The patient creates a compressed volume of air by squeezing the pneumatic handle. Once the device is activated, the powder is released into a visible cloud, where it is suspended in a small volume of air that can be inhaled. A 5-second breath-hold allows the drug to settle in the lungs.

The dose of inhaled insulin is measured in milligrams rather than in units. The manufacturer's guidelines suggest that the initial estimate of the appropriate premeal dose should be 0.05 mg per kilogram of body weight. Thus, a person who weighs 100 kg should take 5 mg of inhaled insulin before each meal. However, unlike subcutaneous insulins, inhaled insulin is currently available in only two fixed doses (1 mg and 3 mg, approximately equivalent to 3 units and 8 units of insulin, respectively). Since only one blister can be used at each inhalation, multiple inhalations before each meal are necessary if the required dose of insulin is not exactly 1 mg or 3 mg. Furthermore, the received dose varies depending on the combination of blisters used. Consecutive inhalation of insulin from three blisters containing 1 mg of insulin apiece causes a 30 to 40% higher insulin exposure than inhalation of insulin from one blister containing 3 mg of insulin. Therefore, patients should not replace a single 3-mg dose with three consecutive 1-mg doses.[38]

Patient education regarding the use of inhaled insulin is critical to maximize the consistency of technique and dose delivery. Maintenance of the inhaler is also essential. The device must be cleaned weekly and allowed to air dry, since moisture in the chamber absorbs the insulin powder. In addition, an internal valve (included with each box of insulin blister packs) must be replaced every 2 weeks; this step requires manual dexterity.

Follow-up should include spirometry at 6 months and then every year because of the potential effect of inhaled insulin on pulmonary function. If the FEV_1 is confirmed to have declined by more than 20% or by more than 500 ml from the baseline value, inhaled insulin should be discontinued indefinitely.[39]

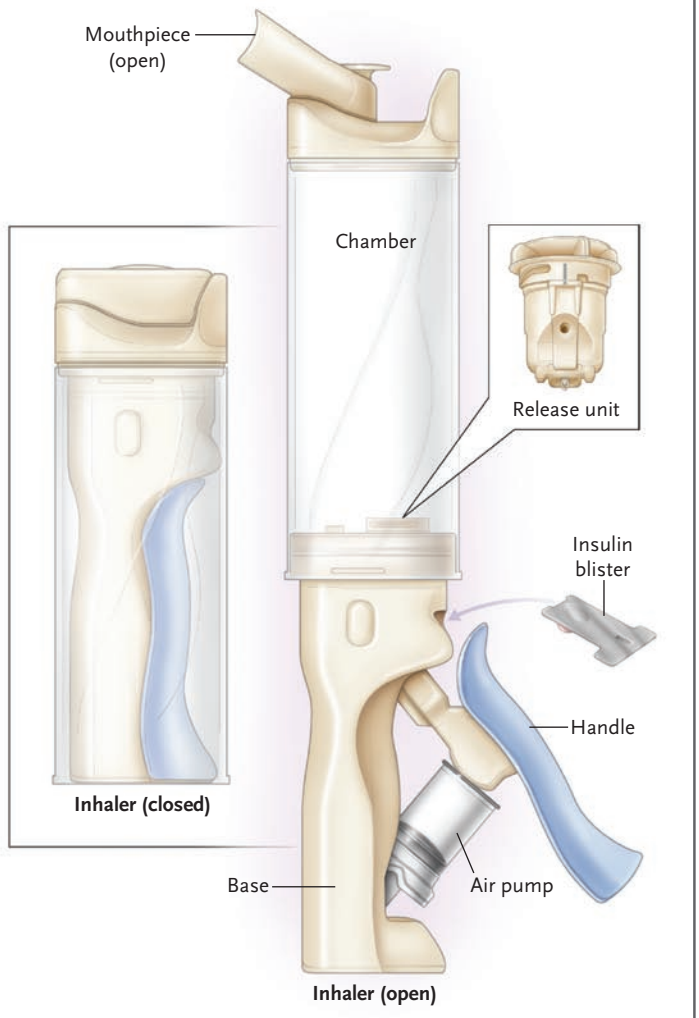

Figure 1. Inhaled Insulin Device.
The Exubera inhaled insulin device is closed for portability and opened before use. It is activated after insertion of an insulin blister. The release unit must be changed every 2 weeks.

Inhaled insulin is more expensive than other mealtime insulin. The average monthly cost of inhaled insulin in the amount recommended for a 100-kg patient is approximately $112.[40] In comparison, the average monthly wholesale cost for a similar dose of injectable insulin is $33 for regular insulin, $76 for a rapid-acting insulin analogue, and $102 for a rapid-acting insulin analogue in a penlike delivery device.[41] Many managed-care organizations offer limited coverage for inhaled insulin, placing it in a tier of medications that require preapproval, higher patient copayments, or both.[40]

ADVERSE EFFECTS

Two studies involving patients with type 1 diabetes and one study involving patients with type 2 diabetes showed a lower overall incidence of hypoglycemia among patients who received inhaled insulin than among those who received injected regular insulin.[25,26,42] However, two of these trials showed an increased incidence of severe hypoglycemia among the patients who received inhaled insulin.[26,42] The rate of hypoglycemia after the use of the Exubera device has not been compared with that associated with the alternative preprandial insulins (aspart, glulisine, or lispro) in head-to-head trials.

Diabetes is associated with abnormal lung function.[43,44] Inhaled insulin has small additional effects on both the diffusing capacity for carbon monoxide and the FEV_1, suggesting effects on the alveolar-capillary membrane and lung elastic recoil, respectively; it is not clear whether these effects are correlated. However, the FEV_1 declined by more than 15% from the baseline value in 1.3% of patients with type 1 diabetes who received inhaled insulin and in 5% of patients with type 2 diabetes who received inhaled insulin. This loss of lung function appeared to resolve within 6 weeks of discontinuation of inhaled insulin after up to 2 years of treatment.[39] It is not known whether these changes in pulmonary function can be predicted on the basis of cough or dyspnea; cough has frequently been reported in clinical trials of inhaled insulin.[25-27,42]

AREAS OF UNCERTAINTY

Insulin acts as a weak growth factor when it binds to the type 1 insulin-like growth factor receptor. Short-term studies in animals have not shown a substantial effect on cell-proliferation indexes in the alveolar or bronchiolar areas of the lung. The long-term effects of supraphysiologic doses of insulin in the human lung or on neoplastic lung tissue are unknown.

Insulin antibody levels rise progressively with the increased duration of exposure to inhaled insulin in patients with type 1 or type 2 diabetes.[25,26,42,45] These levels stabilize within 9 to 12 months after the start of treatment and decline but do not normalize after cessation of treatment.[37] Antibody levels are especially elevated among patients with type 1 diabetes, increasing by

more than a factor of 8 after 6 months of the use of inhaled insulin.[37] The frequency of severe hypoglycemia and the onset or duration of insulin activity have not been shown to be altered in the presence of insulin antibodies,[45] but further study is required to confirm that these antibodies do not act as a reservoir for delayed insulin release.

Studies have suggested that patients with diabetes are likely to prefer inhaled insulin over insulin injection,[31,32] in some cases by a ratio of 8:1.[46] It is not clear whether any increases in patient preference, acceptability, or satisfaction will be translated into increased compliance and improved glucose control. Managed-care companies and patients will need to decide whether they are willing to pay the additional price for this alternative insulin delivery system. Other inhaled insulin systems are in various stages of development and will need to be compared with the Exubera inhalation device. Finally, the longer-term safety and efficacy of this form of therapy have not yet been established.

GUIDELINES

In the United Kingdom, the National Institute for Health and Clinical Excellence recommends that inhaled insulin be prescribed only by diabetes specialists and for patients with needle phobia or severe problems at injection sites.[47] The German Institute for Quality and Efficiency in Health Care has concluded that inhaled insulin offered no additional benefit over subcutaneously administered insulin.[48] No guidelines for the use of inhaled insulin have been developed by expert groups or societies in the United States.

RECOMMENDATIONS

The patient described in the vignette presents with circumstances that are typical of many persons for whom insulin therapy is recommended. Although the concept of inhaled insulin is likely to be attractive to many such patients, we would first target the fasting glucose before introducing a preprandial insulin. After appropriate education and with the necessary support in place, we would begin treatment with a basal insulin given before sleep, adjusting the dose to achieve a mean fasting glucose level of approximately 100 mg per deciliter. Thus, we do not recommend the use of inhaled insulin in this patient. Should the patient later require preprandial insulin, the freedom from subcutaneous injection offered by inhaled insulin should be weighed against the necessity for multiple inhalations (sometimes at each dose), added cost, limited portability, risk of hypoglycemia, and unknown long-term adverse effects of this form of therapy.

No potential conflict of interest relevant to this article was reported.

We thank Christopher H. Fanta, M.D., for helpful comments.

A video showing the use of inhaled insulin is available with the full text of this article at www.nejm.org.

REFERENCES

1. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health and Nutrition Examination Survey 1999-2002. Diabetes Care 2006;29:1263-8.
2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.
3. Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the US in 2002. Diabetes Care 2003;26:917-32.
4. Insulin and diabetes medication use: data and trends from the National Diabetes Surveillance System. Atlanta: Centers for Disease Control and Prevention, 2005. (Accessed January 8, 2007, at http://www.cdc.gov/Diabetes/statistics/meduse/dtltable2.htm.)
5. Summers KH, Szeinbach SL, Lenox SM. Preference for insulin delivery systems among current insulin users and nonusers. Clin Ther 2004;26:1498-505.
6. Richardson T, Kerr D. Skin-related complications of insulin therapy: epidemiology and emerging management strategies. Am J Clin Dermatol 2003;4:661-7.
7. Peyrot M, Rubin RR, Lauritzen T, et al. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care 2005;28:2673-9.
8. Hunt LM, Valenzuela MA, Pugh JA. NIDDM patients' fears and hopes about insulin therapy: the basis of patient reluctance. Diabetes Care 1997;20:292-8.
9. Zambanini A, Newson RB, Maisey M, Feher MD. Injection related anxiety in insulin-treated diabetes. Diabetes Res Clin Pract 1999;46:239-46.
10. Zambanini A, Feher MD. Needle phobia in type 1 diabetes mellitus. Diabet Med 1997;14:321-3.
11. Zambanini A, McIntosh CS, Mitchell C, Catalan J, Feher MD. Psychological issues in diabetes. Lancet 1999;354:74.
12. Freemantle N, Blonde L, Duhot D, et al. Availability of inhaled insulin promotes greater perceived acceptance of insulin therapy in patients with type 2 diabetes. Diabetes Care 2005;28:427-8.
13. Cefalu WT. Novel routes of insulin delivery for patients with type 1 or type 2 diabetes. Ann Med 2001;33:579-86.
14. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA 2003;289:2254-64.
15. Agu RU, Ugwoke MI, Armand M, Kinget R, Verbeke N. The lung as a route for systemic delivery of therapeutic proteins and peptides. Respir Res 2001;2:198-209.
16. Wearley LL. Recent progress in pro-

tein and peptide delivery by noninvasive routes. Crit Rev Ther Drug Carrier Syst 1991;8:331-94.
17. Niven RW. Delivery of biotherapeutics by inhalation aerosol. Crit Rev Ther Drug Carrier Syst 1995;12:151-231.
18. European public assessment report: Exubera. London: European Medicines Agency, 2006. (Accessed January 8, 2007, at http://www.emea.eu.int/humandocs/PDFs/EPAR/exubera/058806en6.pdf.)
19. Patton JS, Bukar J, Nagarajan S. Inhaled insulin. Adv Drug Deliv Rev 1999; 35:235-47.
20. Patton JS, Bukar JG, Eldon MA. Clinical pharmacokinetics and pharmacodynamics of inhaled insulin. Clin Pharmacokinet 2004;43:781-801.
21. Cefalu WT, Skyler JS, Kourides IA, et al. Inhaled human insulin treatment in patients with type 2 diabetes mellitus. Ann Intern Med 2001;134:203-7.
22. Rave K, Bott S, Heinemann L, et al. Time-action profile of inhaled insulin in comparison with subcutaneously injected insulin lispro and regular human insulin. Diabetes Care 2005;28:1077-82.
23. Ceglia L, Lau J, Pittas AG. Meta-analysis: efficacy and safety of inhaled insulin therapy in adults with diabetes mellitus. Ann Intern Med 2006;145:665-75.
24. Statistical review and evaluation of Exubera. Washington, DC: Food and Drug Administration, December 27, 2004. (Accessed January 8, 2007, at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4169B1_02_05-FDA-Clin-Stats-Efficacy.pdf.)
25. Quattrin T, Belanger A, Bohannon NJ, Schwartz SL. Efficacy and safety of inhaled insulin (Exubera) compared with subcutaneous insulin therapy in patients with type 1 diabetes: results of a 6-month, randomized, comparative trial. Diabetes Care 2004;27:2622-7.
26. Hollander PA, Blonde L, Rowe R, et al. Efficacy and safety of inhaled insulin (Exubera) compared with subcutaneous insulin therapy in patients with type 2 diabetes: results of a 6-month, randomized, comparative trial. Diabetes Care 2004;27:2356-62.
27. DeFronzo RA, Bergenstal RM, Cefalu WT, et al. Efficacy of inhaled insulin in patients with type 2 diabetes not controlled with diet and exercise: a 12-week, randomized, comparative trial. Diabetes Care 2005; 28:1922-8.
28. Rosenstock J, Zinman B, Murphy LJ, et al. Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes: a randomized, controlled trial. Ann Intern Med 2005;143:549-58.
29. Barnett AH, Dreyer M, Lange P, Serdarevic-Pehar M. An open, randomized, parallel-group study to compare the efficacy and safety profile of inhaled human insulin (Exubera) with metformin as adjunctive therapy in patients with type 2 diabetes poorly controlled on a sulfonylurea. Diabetes Care 2006;29:1282-7.
30. *Idem.* An open, randomized, parallel-group study to compare the efficacy and safety profile of inhaled human insulin (Exubera) with glibenclamide as adjunctive therapy in patients with type 2 diabetes poorly controlled on metformin. Diabetes Care 2006;29:1818-25.
31. Cappelleri JC, Cefalu WT, Rosenstock J, Kourides IA, Gerber RA. Treatment satisfaction in type 2 diabetes: a comparison between an inhaled insulin regimen and a subcutaneous insulin regimen. Clin Ther 2002;24:552-64.
32. Rosenstock J, Cappelleri JC, Bolinder B, Gerber RA. Patient satisfaction and glycemic control after 1 year with inhaled insulin (Exubera) in patients with type 1 or type 2 diabetes. Diabetes Care 2004; 27:1318-23.
33. FDA approves first ever inhaled insulin combination product for treatment of diabetes. Washington, DC: Food and Drug Administration, January 27, 2006. (Accessed January 8, 2007, at http://www.fda.gov/bbs/topics/news/2006/NEW01304.html.)
34. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26:3080-6.
35. Becker RH, Sha S, Frick AD, Fountaine RJ. The effect of smoking cessation and subsequent resumption on absorption of inhaled insulin. Diabetes Care 2006; 29:277-82.
36. Himmelmann A, Jendle J, Mellen A, Petersen AH, Dahl UL, Wollmer P. The impact of smoking on inhaled insulin. Diabetes Care 2003;26:677-82.
37. Advisory Committee briefing document: Exubera. New York: Pfizer Pharmaceuticals, August 3, 2005. (Accessed January 8, 2007, at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4169B1_01_01-Pfizer-Exubera.pdf.)
38. Exubera. New York: Pfizer, January 2006 (package insert). (Accessed January 8, 2007, at http://www.fda.gov/cder/foi/label/2006/021868lbl.pdf.)
39. Product overview: Exubera. London: European Medicines Agency, January 24, 2006. (Accessed January 8, 2007, at http://www.emea.eu.int/humandocs/Humans/EPAR/exubera/exubera.htm.)
40. Sanderson I, Cacciatore K, Goater J, Scala S, Fernandez S. Exubera pricing more competitive than forecast. New York: S.G. Cowen, June 22, 2006.
41. 2006 Red Book: pharmacy's fundamental reference. Montvale, NJ: Thomson/PDR, 2006.
42. Skyler JS, Weinstock RS, Raskin P, et al. Use of inhaled insulin in a basal/bolus insulin regimen in type 1 diabetic subjects: a 6-month, randomized, comparative trial. Diabetes Care 2005;28:1630-5.
43. Ramirez LC, Dal Nogare A, Hsia C, et al. Relationship between diabetes control and pulmonary function in insulin-dependent diabetes mellitus. Am J Med 1991; 91:371-6.
44. Hsia CC, Raskin P. The diabetic lung: relevance of alveolar microangiopathy for the use of inhaled insulin. Am J Med 2005;118:205-11.
45. Fineberg SE, Kawabata T, Finco-Kent D, Liu C, Krasner A. Antibody response to inhaled insulin in patients with type 1 or type 2 diabetes: an analysis of initial phase II and III inhaled insulin (Exubera) trials and a two-year extension trial. J Clin Endocrinol Metab 2005;90:3287-94.
46. Sadri H, MacKeigan LD, Leiter LA, Einarson TR. Willingness to pay for inhaled insulin: a contingent valuation approach. Pharmacoeconomics 2005;23:1215-27.
47. Inhaled insulin for the treatment of diabetes (types 1 and 2). London: National Institute for Health and Clinical Excellence, December 2006. (Accessed January 8, 2007, at http://www.nice.org.uk/TA113.)
48. Inhaled insulin (Exubera): Rapid Report 01. Cologne, Germany: Institute for Quality and Efficiency in Health Care, April 2006.