

Inhaled Human Insulin (Exubera®): An Opportunity for Improving Long-Term Glycaemic Control in Patients with Diabetes?

a report by

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Diabetes is at epidemic levels, with the costs of treatment placing a significant economic burden on healthcare systems worldwide. Most people with type 2 diabetes are failing to achieve optimal blood glucose control, leading to disease progression and the onset of debilitating and expensive complications, including heart disease, amputations, blindness and kidney failure. To achieve adequate blood glucose control, all patients with type 1 diabetes need exogenous insulin, and most with type 2 diabetes will also eventually require insulin replacement therapy. Despite the fact that insulin is the most effective glucose-lowering treatment available, studies using US and UK medical databases indicate that more than half of the patients who no longer achieve glycaemic control with oral medications wait four years or more to initiate subcutaneous insulin therapy. Fear of needles and the burden associated with multiple daily injections remain among the most significant barriers to initiating and maintaining insulin therapy. Inhaled human insulin (INH; Exubera® (insulin human (rDNA origin)) Inhalation Powder) is a novel, rapid-acting, insulin formulation administered by inhalation before meals. An extensive clinical trial program including studies for up to two years demonstrated the efficacy and safety profile of INH in the treatment of both type 1 and type 2 diabetes. As a non-invasive alternative to subcutaneous insulin,

INH is also associated with increased patient acceptance and treatment satisfaction. Thus, the availability of INH offers the potential to provide improved blood glucose control. Over the long term, better glycaemic control has the potential to reduce the risk of costly diabetic complications.

Current Burden of Diabetes

Diabetes mellitus is a major contributor to the global disease burden with the number of patients growing on an epidemic scale. An estimated 194 million people worldwide are currently affected with diabetes, a figure the World Health Organization (WHO) expects to rise to 366 million cases by 2030.^{1,2} Major landmark clinical studies, such as the UK Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT), have shown that improvement in blood glucose control reduces the risk of development of diabetes-related complications.³⁻⁵ It follows that, the longer a person lives with uncontrolled diabetes, the greater the risk of developing vascular complications, including retinopathy, end-stage renal disease, neuropathy and coronary heart disease.³⁻⁵ Debilitating to the individual, such complications are also expensive to treat. Indeed, the significant majority of the economic healthcare burden of diabetes relates to the treatment and consequences of



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PRESCRIBING INFORMATION

EXUBERA® (inhaled insulin human)

Please refer to Summary of Product Characteristics (SmPC) before prescribing. **Presentation:** EXUBERA is supplied in unit dose blisters containing 1 mg and 3 mg of insulin human. **Indication:** Treatment of adult patients with type 2 diabetes mellitus not adequately controlled with oral antidiabetic agents and requiring insulin therapy. Treatment of adult patients with type 1 diabetes mellitus, in addition to long or intermediate acting subcutaneous insulin, for whom the potential benefits of adding inhaled insulin outweigh the potential safety concerns. **Dosage:** EXUBERA is administered via the lungs by oral inhalation only with the insulin inhaler. A recommended starting daily dose is based on the following formula: Body weight (kg) X 0.15 mg/kg = Total Daily Dose (mg). The total daily dose should be divided into three pre-meal doses. Administration should be within 10 minutes before the start of a meal. 1 mg and 3 mg EXUBERA are approximately equivalent to 3 IU and 8 IU of subcutaneously injected fast-acting human insulin, respectively. Dose adjustment may be required based on the meal size and nutrient composition, time of day, pre-meal blood glucose concentration, recent or anticipated exercise. During intercurrent respiratory illness close monitoring of blood glucose concentrations and dose adjustment may be required. **Hepatic and renal impairment:** insulin requirements may be diminished. **Children and adolescents:** not recommended in patients under 18 years of age. **Elderly:** limited experience in patients ≥ 75 years of age. **Congestive heart failure:** very limited experience and its use is therefore not recommended. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Hypoglycaemia. Poorly controlled, unstable, or severe asthma. Severe (GOLD stage III or IV) COPD. Patients must not smoke during EXUBERA therapy and must have stopped smoking at least 6 months prior to starting therapy. If a patient starts or resumes smoking, EXUBERA must be discontinued immediately due to the increased risk of hypoglycaemia. **Warnings and precautions:** Consecutive inhalation of three 1 mg unit dose blisters causes a significantly higher insulin exposure than inhalation of one 3 mg unit dose blister. Therefore three 1 mg unit dose blisters should not be substituted for one 3 mg unit dose blister. EXUBERA should not be used in patients with lung disease such as asthma and COPD. The use of EXUBERA in patients requiring dose titrations of less than 1 mg is not recommended. EXUBERA should be used with caution in patients of low body weight. **Decline in pulmonary function:** In clinical trials small decline of pulmonary function (particularly Forced Expiratory Volume in one second (FEV₁)) have been observed. There was no accelerated decline beyond 3-6 months and the decline resolved upon discontinuation. All patients initiated on EXUBERA should have a baseline lung function examination (e.g. spirometry to measure FEV₁) and a follow-up measurement after the first 6 months of therapy (see SmPC for more information). Patients developing dyspnoea while treated with EXUBERA should be examined for pulmonary or cardiac causes. Where pulmonary oedema is present, or where there is a clinically relevant reduction in pulmonary function, EXUBERA should be discontinued. Patients must receive comprehensive instructions in the use of the insulin inhaler (see Instructions for Use). A few patients have reported changes in the warning symptoms of hypoglycaemia following the transfer from animal insulin to human insulin. The ability to concentrate may be impaired as a result of hypoglycaemia which may constitute a risk in situations where these abilities are of special importance e.g. driving or operating machinery. **Interactions:** A number of substances affect glucose metabolism and may require dose adjustment of insulin (see SmPC for more information). Active smoking greatly enhances, whereas passive exposure to tobacco smoke in non-smokers decreases the rate and extent of absorption of EXUBERA. **Pregnancy:** There is no clinical experience with EXUBERA use in pregnancy. Inhaled insulin frequently induces insulin antibodies, the risk of which to the foetus is not known. Therefore, EXUBERA should not be used during pregnancy. **Side Effects:** Most commonly (≥ 1/10) reported side effects were: hypoglycaemia and cough. Commonly (≥ 1/100, ≤ 1/10) reported side effects were: dyspnoea, productive cough, throat irritation and dry throat. Bronchospasm may rarely occur. A decline from baseline in FEV₁ was observed in clinical trials. As with other insulins, generalised allergic reactions may occur very rarely. Please refer to SmPC for more information on side effects. **Overdose:** Hypoglycaemia may occur as a result of an excess of insulin relative to food intake, energy expenditure or both. Mild episodes of hypoglycaemia usually can be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes, with coma, seizure, or neurological impairment may be treated with intramuscular/subcutaneous glucagon (0.5 to 1 mg) or concentrated intravenous glucose. **Legal Category:** POM. **Package quantities, Marketing Authorisation numbers and basic NHS price:** EXUBERA 1 mg, 90 unit dose blisters, EU/105/327/003, £25.19; EXUBERA 3 mg, 90 unit dose blisters, EU/105/327/011, £62.28. **Marketing Authorisation Holder:** Pfizer Ltd, Ramsgate Road, Sandwich, CT13 9NU, UK. **Further information** is available via the INH Programme: Tel. 0845 850 0198, www.INHprogramme.co.uk. Medical Information Department, Pfizer Limited, Walton Oaks, Dorking Road, Walton-on-the-Hill, Surrey, KT20 7NS. **Date of Preparation:** May 2006. **Company reference:** EX3_2

Adverse events should be reported to Pfizer Medical Information on 01304 616161. Information about adverse event reporting can also be found at www.yellowcard.gov.uk

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Date of preparation: May 2006

Code: EXU658B

diabetic complications.⁶ The worldwide diabetes-related annual healthcare costs alone have been estimated to be as much as US\$286 billion, accounting for between 2.5% and 15% of a country's healthcare expenditure.^{1,7} Diabetes is also associated with significant indirect costs due to work and productivity losses, disability and premature mortality.⁷ The health benefits of maintaining tight blood glucose control in diabetes are well established. However, despite current treatment options and the widespread adoption of stringent clinical management guidelines, most people with diabetes are not achieving optimal blood glucose control, and are at ongoing risk of serious complications.⁸

Injectable Insulin Therapy

Insulin has long been established as a therapy for controlling blood glucose in people with diabetes and is the most effective glucose lowering agent available to date. Individuals with type 1 diabetes require insulin replacement therapy throughout their lives. Type 2 diabetes is a progressive disease normally resulting from a combination of insulin resistance and progressive beta-cell dysfunction, and is treated by most physicians in a stepwise manner.⁹ Management of type 2 diabetes typically commences with diet and lifestyle interventions, eventually followed by the addition of a single oral anti-diabetic drug and then a combination of oral drugs. However, oral therapy is often not sufficient to achieve appropriate glycaemic control. Recent data from the Kaiser Permanente database suggested that only half the patients achieve targeted glycaemic control when using the combination of sulphonylurea and metformin. Furthermore, even when successful, these patients maintained target control for less than one year and continued suboptimal therapy for 2-3 years before transitioning onto insulin.¹⁰ Therefore, most people with type 2 diabetes will eventually require intensive insulin therapy to achieve adequate blood glucose control.¹¹

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Introducing inhaled insulin

New EXUBERA

- For mealtime glycaemic control^{1,2}
- Maintains long-term glycaemic control³
- Is an insulin treatment patients choose⁴
- Has a dedicated programme of support for patients and healthcare professionals



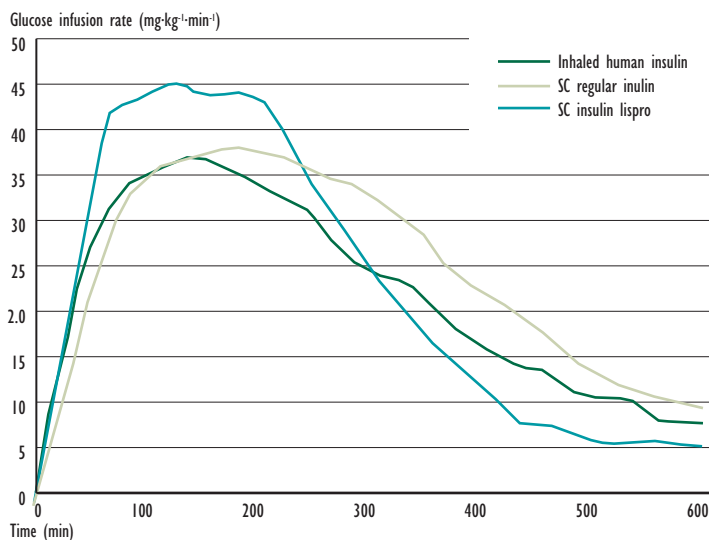
The
new look
of insulin

Prescribing information can be found on the facing page

Changing the diabetes experience


EXUBERA 
inhaled insulin human

Figure 1: Time-action Profile of INH (6mg), Regular Human Insulin (18U) and Insulin Lispro (18U)



Source: Adapted with permission from 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: pp. 1077-1082.

The need for multiple daily insulin injections is burdensome to diabetes sufferers. Typical patient concerns relate to fear of needles and injection pain,

favour of reducing the number of daily injections.¹⁴ Moreover, around one-quarter of people with diabetes reportedly refuse insulin therapy once it is prescribed.^{15,16} Furthermore, physicians also delay prescribing insulin therapy.^{12,13,17} As a result, insulin use may be delayed for years in many patients with type 2 diabetes. In fact, one recent study demonstrated that more than half of the patients who no longer achieve glycaemic control with oral medications wait five years or more to initiate subcutaneous insulin therapy.¹⁸

There is a need to decrease the above risks, improve the long-term health outcomes of diabetes sufferers and lessen the economic burden of disease, and to achieve these aims, additional, non-invasive, insulin-based therapeutic options could be helpful.

Introduction to Inhaled Human Insulin – Demonstrated Clinical Efficacy and Safety

Efforts to develop non-invasive alternatives to injectable insulin began soon after the discovery of insulin. Until recently, issues with insulin

The pulmonary route is the most widely researched non-invasive alternative to subcutaneous administration and offers the greatest potential for systemic insulin delivery.

difficulty with administration, and concerns about side effects, complications and disease progression.^{12,13} These concerns contribute to the barriers to treatment acceptance. This was suitably demonstrated in one study by Hauber and colleagues in which people with type 2 diabetes appeared willing to sacrifice adequate blood glucose control in

bioavailability and the technology required for delivering insulin by alternative routes have hampered progress.¹⁹ The pulmonary route is the most widely researched non-invasive alternative to subcutaneous administration and offers the greatest potential for systemic insulin delivery. Its advantages include a large absorptive surface, high permeability

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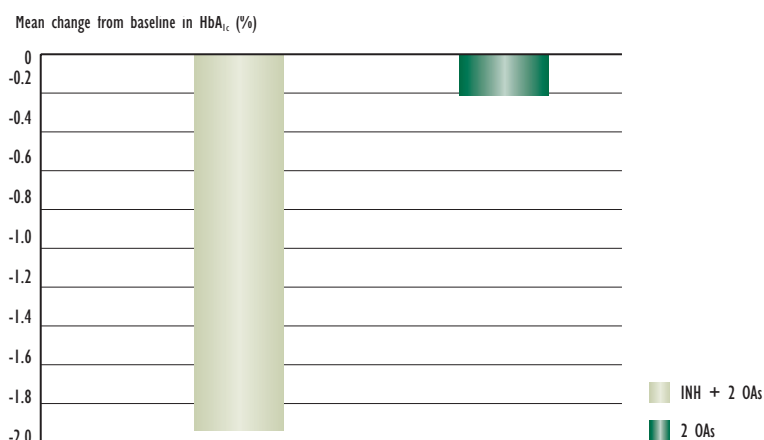
and an extensive vascular network permitting rapid passage of insulin from the alveoli into the systemic circulation.²⁰ Key to the development of novel inhalation systems has been the improvement of insulin formulations and inhalers, such that the inhaled insulin particles are optimally sized for efficient delivery into the deep lung.

Inhaled human insulin (INH; Exubera® (insulin human (rDNA origin)) Inhalation Powder) is the first inhaled insulin product to be approved in the EU and US for the treatment of adults with type 1 or type 2 diabetes. It is the first non-invasive alternative to multiple daily insulin injections since the introduction of insulin 80 years ago. INH is a fast-acting, dry-powder formulation of human insulin intended for use before meals. It is inhaled into the lungs via the mouth through a simple-to-use, mechanical hand-held device that operates without batteries. The pharmacokinetic profile of INH mimics the normal physiological pattern of insulin secretion in response to a meal, with an initial rise in plasma insulin levels similar to rapid-acting insulin analogues, and a duration of action that is comparable to subcutaneous regular insulin (see *Figure 1*).²¹ Therefore, INH administered 10 minutes before meals provides post-meal glucose control.

Efficacy

INH has been evaluated in clinical trials including over 2,700 adults with type 1 and type 2 diabetes, with some treated for up to seven years. In each trial, efficacy has been assessed using glycosylated

Figure 2: Decline from Baseline in HbA1c (%) After 12 Weeks of INH+OA and OA Combination Therapy in Patients Failing Dual OA Therapy



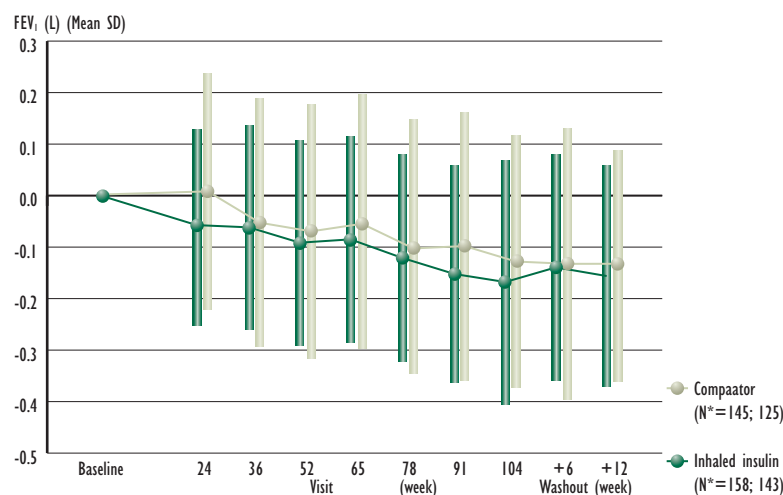
Source: Rosenstock J, Zinman B, Murphy L J, et al., "Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes", *Ann. Intern. Med.* (2005), 143: pp. 549-558.

haemoglobin (HbA1c) as the primary outcome. Comparisons with subcutaneous regimens combining rapid-acting regular insulin and long-acting insulins in subjects with type 1 diabetes have shown that INH provides similar glycaemic control to subcutaneous pre-meal injections as part of a conventional or intensive insulin regimen.²²⁻²⁵

In type 2 diabetes, INH has been compared with oral anti-diabetic agents and with a subcutaneous rapid-acting insulin regimen. When used as an early pharmacological intervention, INH achieves blood glucose control in subjects with type 2 diabetes sub-optimally controlled on diet and exercise.²⁶ Similarly, 2 studies showed that, in patients uncontrolled on a single oral

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Figure 3: Treatment group differences in changes from baseline FEV₁ (L) with INH and OA comparator over a 104-week treatment period, and a 12-week washout phase (no INH)



(*N at baseline and at end of 104 weeks of therapy). [Adapted with permission from Brain JD, "Unlocking the opportunity of tight glycemic control. Inhaled insulin: safety", *Diabetes Obes. Metab.* (2005), 7 (Suppl 1): pp. S14-18.]

agent (HbA_{1c} >9.5%), addition of INH significantly improves glycaemic control compared with adjunctive oral agent therapy.^{27,28} Furthermore, in subjects failing dual oral anti-diabetic therapy, INH provides greater improvements in blood glucose control than continued oral therapy, either administered alone or in addition to existing oral therapy (see *Figure 2*).²⁹ INH is also effective as part of a conventional insulin regimen, achieving levels of blood glucose control comparable to subcutaneous insulin injections.^{30,31}

Secondary outcome assessments of post-meal and fasting glucose concentrations and weight gain are also recognised as important measures of diabetes control. The INH clinical development program has also demonstrated equivalence of reduction of post-meal glucose concentrations and improvement in fasting glucose levels compared with subcutaneous insulins in people with type 1 or type 2 diabetes.^{24,25,30} Less weight gain has also been reported with INH compared with subcutaneous insulin.³⁰

Safety

The safety profile of INH has been extensively studied. Adverse events throughout the clinical development program were generally mild-to-moderate in severity, and discontinuation rates were low. As with all insulin products, hypoglycaemia was the most commonly reported adverse event with severity and incidence similar to those observed with subcutaneous insulin therapy.^{24,25,30} As expected, the incidence of hypoglycaemia was higher with adjunctive INH compared with adjunctive oral anti-diabetic therapy.²⁶⁻²⁹ Cough of mild-to-moderate severity has been observed at a higher frequency in subjects receiving INH compared with subcutaneous insulin. Cough generally occurred within seconds to minutes of INH administration, was rarely productive and decreased with time on therapy.^{24-27,30} Less than 1% of trial subjects discontinued INH due to cough.

Small but consistent treatment group differences in lung function tests (forced expiratory volume in 1 second (FEV₁) and diffusing capacity of carbon monoxide (DL_{CO})) favouring the comparator therapy have been observed with INH. As well as being small, these changes occurred early after treatment initiation, were non-progressive for up to two years and were reversible following discontinuation (see *Figure 3*).^{26,27,30,32} Lung function monitoring is recommended prior to INH initiation and at regular intervals thereafter, in order to detect any unexpected increased effect.

Patient Satisfaction with Treatment

A feature of INH across several clinical studies is its association with greater patient satisfaction compared with subcutaneous insulin in both type 1 and type 2 diabetes.^{24,30,33-36} Subjects receiving INH reported a greater improvement in global treatment satisfaction, convenience/ease of use, and social

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comfort after one year of therapy compared with those who remain on subcutaneous insulin. INH has also been associated with significant improvements in some quality of life scores compared with subcutaneous insulin.^{35,36}

Furthermore, patients commonly prefer INH to subcutaneous insulin. In one study, when subjects with type 1 or type 2 diabetes initially assigned to treatment with INH or subcutaneous insulin were allowed to select a regimen for on-going treatment, most INH-treated subjects (85%) elected to continue with INH. In contrast, most subjects treated initially with subcutaneous insulin choose to switch to INH (75%).³⁷ A further randomised, controlled study of subjects with type 2 diabetes inadequately controlled on diet and/or oral anti-diabetic drugs explored the issue of patient acceptance.³⁸ In this study, the availability of INH as a treatment choice resulted in a three-fold greater number of subjects opting for a treatment that included any insulin compared with subjects offered treatments other than INH.

treatment satisfaction with INH compared to remaining uncontrolled on oral anti-diabetic drugs, or compared to insulin injections. The increased willingness to switch to a more appropriate therapy could lead to the earlier initiation and intensification of insulin therapy, particularly in those patients with type 2 diabetes failing on oral anti-diabetic drugs. A potential outcome of earlier insulin treatment is shorter periods of poor blood glucose control, or conversely, improved blood glucose control in the short and the long term.

Studies such as the UKPDS and DCCT lend support to early and intensive pharmacological intervention. In this regard, insulin, more so than oral anti-diabetic drugs, is effective at controlling post-meal escalations in blood glucose, which have been linked to increased cardiovascular risk.³⁹⁻⁴¹ Clearly, the choice of treatment and the decision when to initiate insulin treatment in particular, could have long-term implications on health outcomes for the patient and healthcare budgets. By offering a non-invasive alternative to injectable insulin, INH may facilitate early and intensive recourse to

Over the long term, improved glycaemic control may lead to reduced risk of diabetes complications and better health outcomes for patients, resulting in reduction in the economic burden of diabetes.

The Potential Role of INH in the Management of Diabetes

A non-invasive alternative to injectable insulin would be a welcome addition to the therapeutic armamentarium in type 1 and type 2 diabetes for both patients and physicians alike. INH has the potential to change the way diabetes is treated by helping to overcome the therapeutic barriers that are associated with administration by injection, thereby increasing patient acceptance of insulin therapy. The clinical trial programme supports this view given that patients reported greater overall preference and

insulin therapy, which may have positive benefits for patient care and healthcare expenditure.

Concluding Remarks

The availability of INH (Exubera®) has the potential to increase insulin acceptance, encouraging earlier initiation and intensification of insulin-based therapeutic regimens, and therefore improving blood glucose control. Over the long term, improved glycaemic control may lead to reduced risk of diabetes complications and better health outcomes for patients, resulting in reduction in the economic burden of diabetes. ■

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