

Inhaled Human Insulin (EXUBERA®)

a report by

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Chantal Mathieu is Professor of Internal Medicine at the University Hospital Gasthuisberg, Catholic University of Leuven, Belgium. In her role as a clinical diabetologist, Dr Mathieu is involved daily in the treatment of patients with type 1 or type 2 diabetes. Her main basic research interests focus on the pathogenesis and prevention of type 1 diabetes, as well as islet transplantation. Dr Mathieu is also active in the clinical organization of diabetes care and patient education. She is the author or co-author of more than 100 peer-reviewed research papers and she is currently the President of the Flemish Diabetes Society. Dr Mathieu graduated from the University of Leuven as MD in 1988 and subsequently went on to study for a PhD examining pathogenetical and therapeutical aspects of immune intervention in animal models of type 1 diabetes.

Since the discovery of insulin in 1922, there have been attempts to develop alternative methods of administration to injection, as it was soon realised that this was a major issue for both patients and physicians.^{1,2} To avoid multiple injections, oral antidiabetic agents and slow-acting insulins were developed. It was only with the publication of the Diabetes Control and Complications Trial³ and the United Kingdom Prospective Diabetes Study (UKPDS),⁴ which highlighted the crucial importance of tight glycaemic control in the prevention of diabetic complications, that insulin gained in popularity once again. The UKPDS trial also illustrated how, because of the progressive nature of type 2 diabetes mellitus, the majority of patients will eventually require a treatment strategy that includes insulin. However, the obstacle of injections remains a frequent deterrent to starting insulin therapy⁵⁻⁷ and has been linked to reduced treatment adherence in both patients with type 1 and type 2 diabetes mellitus.

After years of intensive research and groundbreaking industrial achievements there are now several insulin inhalation systems at varying stages of clinical development.⁸ Two major forms of pulmonary insulin are being developed: powder and liquid formulas. All have a time-action profile similar to short-acting human insulin, with a slightly more rapid onset of action.^{8,9} A crucial player in this field is inhaled human insulin (Exubera®). Developed by Pfizer Inc in collaboration with Nektar Therapeutics, Exubera® is the first inhaled insulin to be approved in both the USA and European Union for the treatment of type 1 and type 2 diabetes mellitus in adults and is supported by a sound clinical dossier of phase 3 trials in patients with type 1^{10,11} and with type 2 diabetes.¹²⁻¹⁵ While a pulmonary insulin will clearly be an advantage for patients with type 1 diabetes who require multiple daily injections to survive, it is likely to be especially beneficial for patients with type 2 diabetes. Recent studies have shown considerable delays in the uptake of subcutaneous insulin therapy by people with type 2 diabetes uncontrolled with multiple oral agents.^{16,17} The

availability of an alternative method of administration to injection in a growing population of patients with type 2 diabetes may be crucial to promote the timely use of insulin and thus the achievement of better glycaemic control earlier in the disease course.

Published trials to date show patients have a greater preference for an inhaled compared with a subcutaneous insulin,¹⁸ and published data for Exubera® have demonstrated good efficacy and an acceptable safety profile.^{10,15,19,20} It is clear that inhaled insulin can be used as an alternative to short-acting insulin, with the expected efficacy of a mealtime insulin and consequent reductions in HbA1c. As with other insulins, hypoglycaemia is also observed with inhaled insulin. Other aspects of the safety profile of inhaled insulin appear reassuring,^{19,20} but, with the advent of a pulmonary route of delivery, endocrinologists must now also monitor the lung. Short-term tolerability results are good, but long-term data (greater than five years administration) are required. A final caveat is that the only trials available at present are industry-sponsored, and most of these have been performed with Exubera®. Some may take for granted that all inhaled insulins will behave similarly, but this may be a premature conclusion and each product should be considered in its own right.

An important issue is whether healthcare systems will be willing to cover reimbursement of inhaled insulins. When using our usual parameters for evaluating added value for a new drug in diabetes treatment, HbA1c lowering is the gold standard. And there, as expected, short-acting insulin, whether injected or inhaled, behaves the same. So, the question is, are we willing to pay extra for the avoidance of injections?

This is a sensitive area where remarks by payers (without diabetes) such as 'Why don't they just inject themselves?' are offending to many patients with diabetes who repeat this daily ritual and are only too aware of the burden of injecting. A more relevant discussion is: what is the real added value?

We have to weigh the benefits versus the potential down sides of the treatment. Among the down sides are the cost and the unknown effects of this route of insulin administration over decades of use. Although there are currently no indications to suggest a cause for concern, caution is necessary and careful long-term follow up of users will be necessary.

On the positive side, the availability of Exubera® in the treatment arsenal may change the fate of patients with type 2 diabetes. Indeed, having the option of inhaled insulin available (perhaps even for limited periods of time due to cost reasons) might

encourage more individuals over the hurdle of initiating insulin. A study by Freemantle et al. has clearly demonstrated that patients with type 2 diabetes would be more likely to accept insulin as part of their treatment regimen if an agent such as Exubera were an option.²¹ A shift in HbA1c levels towards current targets by more timely use of insulin would have a major impact on diabetes-related complications and quality of life and should be taken into account when discussing reimbursement of inhaled insulin. This of course requires integrated visions on diabetes care and healthcare as a whole. ■

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