



## Complete Summary

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### GUIDELINE TITLE

Inhaled insulin for the treatment of diabetes (types 1 and 2).

### BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Inhaled insulin for the treatment of diabetes (types 1 and 2). London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Dec. 34 p. (Technology appraisal; no. 113).

### GUIDELINE STATUS

This is the current release of the guideline.

## \*\* REGULATORY ALERT \*\*

### FDA WARNING/REGULATORY ALERT

**Note from the National Guideline Clearinghouse:** This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [April 10, 2008, Exubera \(insulin inhalation\)](#): Pfizer informed healthcare professionals and patients of updated safety information in the WARNINGS section of prescribing information for Exubera. This warning relates to a small number of primary lung malignancies that have been discovered in users of Exubera in clinical trials and post-marketing reports.

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## SCOPE

### **DISEASE/CONDITION(S)**

Diabetes (types 1 and 2)

### **GUIDELINE CATEGORY**

Assessment of Therapeutic Effectiveness  
Management  
Treatment

### **CLINICAL SPECIALTY**

Endocrinology  
Family Practice  
Internal Medicine

### **INTENDED USERS**

Advanced Practice Nurses  
Nurses  
Physician Assistants  
Physicians

### **GUIDELINE OBJECTIVE(S)**

To assess the clinical and cost effectiveness of one short-acting inhaled insulin, Exubera, in the management of type 1 or type 2 diabetes mellitus

### **TARGET POPULATION**

Patients with type 1 or type 2 diabetes mellitus

### **INTERVENTIONS AND PRACTICES CONSIDERED**

Short-acting inhaled insulin, Exubera

### **MAJOR OUTCOMES CONSIDERED**

- Clinical effectiveness
  - Glycaemic control, as measured by glycated haemoglobin
  - Hypoglycaemia, weight change, and other adverse events
  - Patient satisfaction
  - Quality of life
- Cost effectiveness

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases  
Searches of Unpublished Data

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

**Note from the National Guideline Clearinghouse (NGC):** The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the University of Aberdeen (See the "Availability of Companion Documents" field.)

#### Clinical Effectiveness

##### Methods for Reviewing Effectiveness

The a priori methods for the review were outlined in the research protocol sent to NICE and presented at the consultees meeting. The methods are summarized below.

Preliminary searches identified that the main comparators in trials to date have been with various injected insulin regimens and against oral combination therapy. The Assessment Group did not consider inhaled insulin to be an alternative to continued oral therapy in patients with type 2 diabetes mellitus, but only for individuals who were not controlled on oral therapy and required some sort of insulin regimen. The Assessment Group were therefore interested in comparisons of inhaled short-acting insulin, versus any injected insulin regimen, or with insulin injected by continuous subcutaneous insulin infusion. The Assessment Group included studies in people with diabetes mellitus requiring insulin therapy, whether type 1 or type 2.

Only randomised controlled trials with parallel groups and controlled cross-over trials were considered eligible. Blinding in trials of this nature would be extremely difficult due to the need to adjust dosage, and while theoretically possible, is impractical. As glycated haemoglobin is an objective measure, this outcome should not be affected by lack of blinding. However, outcomes such as patient satisfaction and quality of life are vulnerable to bias as a result of the lack of blinding and any differences must be interpreted with caution.

The minimum trial duration considered eligible was 10 weeks, based on the time taken for glycated haemoglobin to reliably reflect changes in glycaemic control. For patient acceptability, longer trial duration is desirable—say adherence at 12 months—but results from shorter durations were included as preliminary searches showed that data from longer periods were not available. For long term

pulmonary effects an uncertain period, probably of at least several years, would be required.

Glycaemic control, as measured by glycated haemoglobin and as a proxy for long-term complications of diabetes, was taken as the primary outcome of interest. The Assessment Group also sought information about patient satisfaction, quality of life, hypoglycaemia, weight change, and other adverse events.

The search strategy is summarised in Appendix 1 of the Assessment Report (see "Availability of Companion Documents" field) and included electronic databases (Medline, Embase, Science Citation Index, BIOSIS, Web of Science Proceedings), the National Research Register, Cochrane Library, Current Controlled Trials and hand searching of recent issues of relevant diabetes journals. The web sites of the American Diabetes Association and the European Association for the Study of Diabetes were searched for recent meeting abstracts.

Pfizer provided copies of posters of studies for which abstracts had been identified from the Assessment Group's search; the posters gave much more detail. One study, cited in the manufacturers submission (Trial 217-1022), is on-going and the data (interim 12 month data) are not currently published. Its primary outcome is lung function change and the Assessment Group have, therefore, summarised it in the Assessment Report (see "Availability of Companion Documents" field) in the relevant section as "additional information".

## **NUMBER OF SOURCE DOCUMENTS**

### **Clinical Effectiveness**

The Assessment Group identified five randomised controlled trials (RCTs) in type 1 diabetes and two in type 2 diabetes. The manufacturer identified the same studies in type 1 and type 2 diabetes. In addition, the manufacturer added one Phase II trial and one unpublished study in type 1 diabetes.

### **Cost Effectiveness**

The Assessment Group and the manufacturer's submission did not identify any published cost-effectiveness studies on inhaled insulin. The manufacturer's submission provided an economic analysis.

## **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Expert Consensus

## **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

Not applicable

## **METHODS USED TO ANALYZE THE EVIDENCE**

Meta-Analysis of Randomized Controlled Trials  
Review of Published Meta-Analyses  
Systematic Review with Evidence Tables

## **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

**Note from the National Guideline Clearinghouse (NGC):** The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the University of Aberdeen (See the "Availability of Companion Documents" field.)

### **Clinical Effectiveness**

All retrieved titles and abstracts were reviewed independently by two researchers. Full papers were retrieved and reviewed by two reviewers independently, using a predefined data extraction form, if the information given suggested that the study:

1. Included diabetic patients treated with insulin (either type 1 or type 2)
2. Compared inhaled insulin with insulin injected subcutaneously
3. Assessed one or more relevant clinical outcomes

Quality assessment of the trials was done using the methods described in the manual of the Centre for Reviews and Dissemination, for randomised controlled trials (RCTs) and controlled clinical trials, and Jadad and Spitzer.

See section 4.1 and 4.3 in the original guideline document for more information about the analysis of the evidence.

### **Cost Effectiveness**

Both the manufacturer's analysis and the Assessment Group's model contained various sensitivity analyses, which used different assumptions on discount rate, costs data, compliance data and uptake of insulin.

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

### **Considerations**

Technology appraisal recommendations are based on a review of clinical and economic evidence.

### **Technology Appraisal Process**

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

### **Who is on the Appraisal Committee?**

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

Not applicable

## **COST ANALYSIS**

### **Cost Effectiveness**

- The Appraisal Committee reviewed evidence from the original manufacturer's economic analysis, the Assessment Groups analysis and the remodelling provided by the manufacturer.
- The Committee discussed the analyses of the cost effectiveness of inhaled insulin. The Committee concluded that because inhaled insulin is more expensive than injected short-acting insulin but not more clinically effective, overall it was not an effective use of National Health Service (NHS) resources in the routine setting. The Committee therefore explored other factors that could potentially improve the cost effectiveness of inhaled insulin. Additionally, the Committee explored if there were any subgroups of people with diabetes who could gain greater clinical benefit from inhaled insulin.
- The Committee noted from the manufacturer's submission that improved patient satisfaction and preference could lead to a more cost-effective use of inhaled insulin. The Committee agreed that these factors would only be relevant to the cost effectiveness if they translated into either: (1) proven changes in health-related quality of life and utility gain, or (2) proven earlier uptake of insulin or intensification of current injection regimen and therefore improved glycaemic control in people with poorly controlled diabetes, with consequent improvements in health outcomes associated with better diabetes control.
- The Committee concluded that the case for cost effectiveness in the general population of people with diabetes was not supported. The Committee was, however, persuaded that inhaled insulin could be cost effective in those people with diabetes who are unable to inject because they experience marked and persistent fear of injections or because they cannot find suitable injection sites (for example, due to severe lipohypertrophy) which cannot be overcome by patient support and education or by injection site rotation.

See Sections 4.2 and 4.3 of the original guideline document for a detailed discussion of the cost-effectiveness analysis and consideration of the evidence.

## **METHOD OF GUIDELINE VALIDATION**

External Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

1. Inhaled insulin is not recommended for the routine treatment of people with type 1 or type 2 diabetes mellitus.
2. Inhaled insulin may be used as a treatment option for people with type 1 or type 2 diabetes mellitus who show evidence of poor glycaemic control despite other therapeutic interventions (including, where appropriate, diet, oral hypoglycaemic agents [OHAs], and subcutaneous insulin) and adequate educational support, **and** who are unable to initiate or intensify preprandial subcutaneous insulin therapy because of either:
  - A marked and persistent fear of injections that meets Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) criteria for specific phobia "blood injection injury type" diagnosed by a diabetes specialist or mental health professional
  - Severe and persistent problems with injection sites (for example, as a consequence of lipohypertrophy) despite support with injection site rotation.
3. In patients receiving inhaled insulin under the circumstances set out in section 2, treatment should only be continued beyond 6 months, and in the longer term, if there is evidence of a sustained improvement in glycated haemoglobin (HbA1c) that is judged to be clinically relevant to the individual patient's overall risk of developing long-term complications of diabetes.
4. Initiation of inhaled insulin treatment and monitoring of response should be carried out at a specialist diabetes centre. The responsible clinician should discuss the risks and benefits of inhaled insulin with the patient so that an informed choice can be made regarding appropriate options for diabetes management, including psychological support and therapy for needle phobia if necessary.
5. Data on the use of inhaled insulin according to this guidance should be collected as part of a coordinated prospective observational study. The data collected should include individual patient outcomes, adverse events, and measurements of lung function.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Appropriate use of inhaled insulin for the treatment of diabetes (types 1 and 2) for improved blood glucose control, patient satisfaction, and quality of life in specified sub-populations (see the "Major Recommendations" field).

## **POTENTIAL HARMS**

The most commonly observed side effects of inhaled insulin are hypoglycaemia and mild cough, the latter of which appears to decrease over time. There is also concern about whether lung damage might occur with long-term use. It is stated in the 'Summary of Product Characteristics' (SPC) that people with diabetes must have stopped smoking at least 6 months before starting treatment and must not smoke during therapy.

For full details of side effects and contraindications, see the Summary of Product Characteristics, available at <http://emc.medicines.org.uk/>.

## **CONTRAINDICATIONS**

### **CONTRAINDICATIONS**

Exubera is contraindicated in people with poorly controlled, unstable or severe asthma, or severe chronic obstructive pulmonary disease. The 'Summary of Product Characteristics' (SPC) also states that Exubera should not be used during pregnancy.

For full details of side effects and contraindications, see the Summary of Product Characteristics, available at <http://emc.medicines.org.uk/>.

## **QUALIFYING STATEMENTS**

### **QUALIFYING STATEMENTS**

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

## **IMPLEMENTATION OF THE GUIDELINE**

### **DESCRIPTION OF IMPLEMENTATION STRATEGY**

#### **Implementation**

- The Healthcare Commission assesses the performance of National Health Service (NHS) organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and

resources for medicines and treatments that have been recommended by National Institute for Health and Clinical Excellence (NICE) technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

- 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website ([www.nice.org.uk/TA113](http://www.nice.org.uk/TA113)) (see also "Availability of Companion Documents" field).
  - Local costing template incorporating costing report to estimate the savings and costs associated with implementation.
  - Audit criteria to monitor local practice.

## **IMPLEMENTATION TOOLS**

Audit Criteria/Indicators  
Patient Resources  
Quick Reference Guides/Physician Guides  
Resources

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

## **INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES**

### **IOM CARE NEED**

Living with Illness

### **IOM DOMAIN**

Effectiveness  
Patient-centeredness

## **IDENTIFYING INFORMATION AND AVAILABILITY**

### **BIBLIOGRAPHIC SOURCE(S)**

National Institute for Health and Clinical Excellence (NICE). Inhaled insulin for the treatment of diabetes (types 1 and 2). London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Dec. 34 p. (Technology appraisal; no. 113).

## **ADAPTATION**

Not applicable: The guideline was not adapted from another source.

## **DATE RELEASED**

2006 Dec

## **GUIDELINE DEVELOPER(S)**

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

## **SOURCE(S) OF FUNDING**

National Institute for Health and Clinical Excellence (NICE)

## **GUIDELINE COMMITTEE**

Appraisal Committee

## **COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE**

*Committee Members:* Dr Jane Adam, Radiologist, St George's Hospital, London; Dr Amanda Adler, Consultant Physician, Addenbrooke's Hospital, Cambridge; Professor A E Ades, MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol; Dr Tom Aslan, General Practitioner, Stockwell, London; Professor David Barnett (*Chair*) Professor of Clinical Pharmacology, University of Leicester; Mrs Elizabeth Brain, Lay Member; Dr Karl Claxton, Health Economist, University of York; Dr Richard Cookson, Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice, University of East Anglia; Mrs Fiona Duncan, Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool; Professor Christopher Eccleston, Director, Pain Management Unit, University of Bath; Dr Paul Ewings, Statistician, Taunton & Somerset NHS Trust, Taunton; Professor John Geddes, Professor of Epidemiological Psychiatry, University of Oxford; Mr John Goulston, Director of Finance, Barts and the London NHS Trust; Mr Adrian Griffin, Health Outcomes Manager, Johnson & Johnson Medical Ltd; Ms Linda Hands, Consultant Surgeon, John Radcliffe Hospital; Dr Elizabeth Haxby, Lead Clinician in Clinical Risk Management, Royal Brompton Hospital; Dr Rowan Hillson, Consultant Physician, Diabeticare, The Hillingdon Hospital; Dr Catherine Jackson, Clinical Senior Lecturer in Primary Care Medicine, University of Dundee; Professor Richard Lilford, Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham; Dr Simon Mitchell, Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester; Ms Judith Paget, Chief Executive, Caerphilly Local Health Board, Hengoed; Dr Katherine Payne, Health Economist, The North West Genetics Knowledge Park, The University of Manchester; Dr Ann Richardson, Independent Research Consultant; Dr Stephen Saltissi, Consultant Cardiologist, Royal Liverpool University Hospital; Mr Mike Spencer, General Manager, Clinical Support Services, Cardiff and Vale NHS Trust; Professor Andrew Stevens (*Vice Chair*) Professor of Public Health,

University of Birmingham; Dr Cathryn Thomas, General Practitioner, and Associate Professor, Department of Primary Care & General Practice, University of Birmingham; Dr Norman Vetter, Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff; Professor Mary Watkins, Professor of Nursing, University of Plymouth; Dr Paul Watson, Medical Director, Essex Strategic Health Authority, Chelmsford

## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

## **GUIDELINE STATUS**

This is the current release of the guideline.

## **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) format from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

## **AVAILABILITY OF COMPANION DOCUMENTS**

The following are available:

- Inhaled insulin for the treatment of diabetes (types 1 and 2). Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Dec. 2 p. (Technology appraisal 113). Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Inhaled insulin for the treatment of diabetes (types 1 and 2). Audit criteria. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Dec. 7 p. (Technology appraisal 113). Available in Portable Document Format (PDF) from the [NICE Web site](#).
- Inhaled insulin for the treatment of diabetes (types 1 and 2). Costing template and report. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Dec. 7 p. (Technology appraisal 113). Electronic copies: Available from the [NICE Web site](#).
- The clinical effectiveness and cost effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation. Assessment report. Health Technology Assessment (HTA) Program. University of Aberdeen. 2006 Jan. Electronic copies: Available from the [NICE Web site](#).

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1157. 11 Strand, London, WC2N 5HR.

## **PATIENT RESOURCES**

The following is available:

- Inhaled insulin for the treatment of type 1 and type 2 diabetes. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Dec. 4 p. (Technology appraisal 113).

Electronic copies: Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

Print copies: Available from the NHS Response Line 0870 1555 455. ref: N1158. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

## **NGC STATUS**

This NGC summary was completed by ECRI on April 4, 2007. This summary was updated by ECRI Institute on April 21, 2008 following the U.S. Food and Drug Administration advisory on Exubera (insulin human rDNA origin) Inhalation Powder.

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