NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Human insulin powder for inhalation (Afrezza) for treating type 1 and type 2 diabetes

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of human insulin powder for inhalation (Afrezza) within its licensed indication for treating type 1 and type 2 diabetes.

Background

Diabetes mellitus is a chronic metabolic disorder characterised by elevated blood glucose levels (hyperglycaemia) resulting from a lack of the hormone insulin or resistance to its action. There are two major types of diabetes. Type 1 diabetes results from an absolute loss of insulin production and therefore administration of insulin is necessary for survival. Type 2 diabetes results from reduced insulin secretion or reduced tissue sensitivity to insulin (known as insulin resistance). If not managed effectively, diabetes mellitus can lead to kidney failure, blindness, limb amputation, and damage to the nervous system, peripheral vasculature and skin. Cardiovascular disease is the most common complication of type 2 diabetes and is the greatest cause of morbidity and premature death. Life expectancy is reduced by up to 10 years in people with diabetes.

There were approximately 2.7 million people in England with diagnosed diabetes mellitus in 2013, of whom 90% had type 2 diabetes. However, many people with type 2 diabetes are undiagnosed, and so the number of people with the condition may be higher than reported. The UK prevalence of type 2 diabetes is rising because of increased prevalence of obesity, decreased physical activity and increased life expectancy after diagnosis because of better cardiovascular risk protection. Type 2 diabetes is particularly prevalent in people of African, South Asian and Caribbean family origin. Type 1 diabetes can develop at any age but usually appears before the age of 40, and especially in childhood.

For the management and treatment of type 1 diabetes, NICE clinical guideline 15 recommends diet and lifestyle advice and a personalised multiple daily insulin injection regimen. A common regimen is the use of short-acting insulin at meal times (bolus), plus long-acting insulin once or twice a day to achieve a steady-state level (basal), known as a bolus-basal regimen. NICE technology appraisal 53 recommends insulin glargine (a long-acting insulin) as a treatment option. NICE technology appraisal 151 recommends continuous subcutaneous insulin infusion or ‘insulin pump' therapy as a possible treatment for adults and children 12 years if: attempts to reach target

haemoglobin A1c (HbA1c) levels with multiple daily injections result in the person having ‘disabling hypoglycaemia', or; HbA1c levels have remained high (8.5% or above) with multiple daily injections (including using long-acting insulin analogues if appropriate), despite the person and/or their carer carefully trying to manage their diabetes.

For the management and treatment of type 2 diabetes, NICE clinical guideline 66 recommends dietary advice and increasing physical activity. If blood glucose is not adequately controlled by diet and nutrition advice alone, the guideline recommends initial drug treatment with either metformin, a sulfonylurea, or acarbose. If dual drug therapy is needed, NICE guidance recommends using a thiazolidinedione (NICE clinical guideline 87), a DPP-4 inhibitor (NICE clinical guideline 87), or dapagliflozin (NICE technology appraisal 288) as an add-on to the initial treatment drug. Insulin therapy is recommended if blood glucose is not adequately controlled with dual therapy (NICE clinical guidelines 66 and 87). If insulin is not appropriate, triple therapy using sitagliptin (NICE clinical guideline 87), a thiazolidinedione (NICE clinical guideline 87), or a GLP-1 mimetic (NICE clinical guideline 87, NICE technology appraisal 203 and NICE technology appraisal 248) as an add-on to dual therapy is recommended.

If insulin therapy is used for the treatment of people with type 2 diabetes, it is recommended that metformin, sulfonylurea or acarbose are continued, and that other drugs are continued only if they are licensed for use with insulin. NICE clinical guideline 87 recommends human neutral protamine Hagedorn (NPH) insulin (an intermediate-acting insulin) as an initial insulin treatment. The guideline recommends switching to a long-acting insulin analogue if a person cannot use the device needed to inject NPH insulin or if there is significant hypoglycaemia. For other people with type 2 diabetes using insulin, it recommends that pre-mixed preparations of short- and intermediate-acting insulin or insulin analogues are considered. The guideline also recommends that people with manual or visual disabilities who require insulin are offered a device (such as a pen injector and cartridge or disposable pen) that takes into account their individual needs.

The technology

Human insulin powder for inhalation (Afrezza, MannKind) is a drug-device combination product consisting of a dry powder formulation of recombinant human insulin and fumaryl diketopiperazine, pre-metered into single use dose cartridges and an inhaler.

Human insulin powder for inhalation (Afrezza) does not currently have a marketing authorisation in the UK for treating type 1 or type 2 diabetes. It has been studied in clinical trials in combination with subcutaneous basal injection compared with usual care (subcutaneous injections of insulin or insulin analogue in combination with subcutaneous basal injection) in adults aged 18 and over with type 1 diabetes. It has also been studied both alone or as an add-on to oral diabetic drugs compared with oral diabetic drugs alone or

subcutaneous injections of insulin or insulin analogue in adults aged 18 and older with type 2 diabetes.

Intervention	Human insulin powder for inhalation (Afrezza)
Populations	Adults with type 1 diabetes Adults with type 2 diabetes for whom insulin is appropriate.
Comparators	For type 1 diabetes mellitus • Subcutaneously injected short-acting insulin • Subcutaneously injected short-acting insulin analogue • Continuous subcutaneous insulin infusion (CSII or insulin pump therapy) For type 2 diabetes mellitus • Subcutaneously injected short-acting insulin • Subcutaneously injected short-acting insulin analogue
Outcomes	The outcome measures to be considered include: • mortality • complications of diabetes, including cardiovascular, renal and eye • HbA1c/glycaemic control • body mass index • frequency and severity of hypoglycaemia • incidence of diabetic emergencies, such as diabetic ketoacidosis, requiring hospitalisation • changes in cardiovascular risk factors • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows, people with a phobia of needles will be considered as a subgroup. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 288, Jun 2013, 'Dapagliflozin in combination therapy for treating type 2 diabetes'. Review Proposal Date Dec 2014 Technology Appraisal No. 248, Feb 2012, 'Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes'. To be updated within update of CG87. Technology Appraisal No. 203, Oct 2010, 'Liraglutide for the treatment of type 2 diabetes mellitus'. To be updated within update of CG87. Technology Appraisal No. 151, Jul 2008, 'Continuous subcutaneous insulin infusion for the treatment of diabetes (review of TA57)'. Guidance on static list. Technology Appraisal No. 53, Dec 2002, 'The clinical and cost effectiveness of long acting insulin analogues for diabetes'. Guidance on static list (replaced by CG66 and CG87). Technology Appraisal in Preparation, 'Buccal insulin for the management of type 1 diabetes'. Earliest anticipated date of publication: TBC. Related Guidelines: Clinical Guideline No. 87, May 2009, 'Type 2 diabetes –

	newer agents (partial update of CG66)'. Review in preparation. Publication date Aug 2015. Clinical Guideline No. 66, May 2008, 'Type 2 diabetes: the management of type 2 diabetes (update)'. Review in preparation. Publication date Aug 2015. Clinical guideline No. 15, Jul 2004, 'Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults'. Update in progress. Earliest anticipated date of publication Aug 2015. Clinical Guideline G, Oct 2002, 'Management of type 2 diabetes – managing blood glucose levels'. Replaced by CG66 and CG87. Clinical guideline in preparation, 'Type 1 diabetes'. Earliest anticipated date of preparation Aug 2015. Related Interventional Procedures: Interventional procedure guideline No. 257, Apr 2008, 'Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus'. Related Quality Standards: Quality Standard No. 6, Mar 2011, 'Diabetes in adults'. Related NICE Pathways: NICE Pathway: Diabetes, Pathway created: May 2011: https://pathways.nice.org.uk/pathways/diabetes
Related National Policy	National Service Framework: Diabetes, Dec 2001. https://www.gov.uk/government/publications/national-service-framework-diabetes NHS England Manual for Prescribed Specialised Services 'Insulin-resistant diabetes service (adults and children)', section 67. http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf The national Program of Care for Internal Medicine (group A) covers 'Specialised Diabetes', which includes people with insulin-resistant diabetes. http://www.england.nhs.uk/ourwork/commissioning/spec-services/npc-crg/group-a/a17/

Questions for consultation

Have all relevant comparators for human insulin powder for inhalation (Afrezza) been included in the scope? Which treatments are considered to be established clinical practice in the NHS for type 1 and type 2 diabetes?

Is the subgroup suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom human insulin powder for inhalation (Afrezza) is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider human insulin powder for inhalation (Afrezza) will fit into the existing NICE pathway, Diabetes?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which human insulin powder for inhalation (Afrezza) will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider human insulin powder for inhalation (Afrezza) to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of human insulin powder inhalation (Afrezza) can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Guide-to-the-single-technology-appraisal-process.pdf)