



ABCD position statement on incretin mimetics and DPP-4 inhibitors – 2009

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Background

Exenatide, an injectable incretin mimetic, was licensed for use in the treatment of type 2 diabetes in the UK in March 2007, in combination with metformin (MF) and/or sulphonylureas (SU) in patients who have inadequate glycaemic control on maximally tolerated doses of these drugs. A second incretin mimetic, liraglutide, and an extended-release exenatide preparation are scheduled for licensing in 2009. Sitagliptin, an oral dipeptidyl peptidase-4 (DPP-4) inhibitor was licensed for use in the UK at the same time in combination with MF and/or glitazones in patients who have inadequate glycaemic control on maximally tolerated doses of these drugs. This indication was extended in January 2008 to include combination with an SU and with both MF and an SU. A second DPP-4 inhibitor, vildagliptin, was licensed in the UK in September 2007 for use in combination with MF or glitazones or an SU in patients with inadequate glycaemic control on maximally tolerated doses of these drugs.

NICE recommendations

In May 2008, National Institute for Health and Clinical Excellence (NICE) type 2 diabetes clinical guidelines recommended that exenatide should only be considered for type 2 diabetes if *all* of the following apply:¹

- BMI >35 in those of European descent, with appropriate adjustment in tailoring this advice for other ethnic groups.
- Specific problems of a psychological, biochemical or physical nature arising from high body weight.

ABSTRACT

The Association of British Clinical Diabetologists (ABCD) currently recommends a limited place for exenatide and the gliptins in obese type 2 diabetes. Exenatide requires careful patient selection and continued specialist support, particularly to avoid initiation in individuals at risk of pancreatitis or for those who are already on insulin therapy. Hypoglycaemic and weight reduction efficacy may vary depending on baseline levels of HbA_{1c} and body mass index. Continuation of therapy beyond six months should be determined by changes in weight and/or HbA_{1c}. Gliptins should be reserved for less obese, less hyperglycaemic cases than those considered for exenatide, assuming normal hepatorenal function, and where sulphonylureas and glitazones are inappropriate. Gliptin therapy should only continue beyond six months if HbA_{1c} levels fall by at least 0.5%. Copyright © 2009 John Wiley & Sons.

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KEY WORDS

type 2 diabetes; incretin mimetics; gliptins; ABCD

- Inadequate blood glucose control (HbA_{1c} >7.5%) with conventional oral agents after a trial of MF and SU.
- Other high cost medication, such as glitazone or insulin injection therapy, would otherwise be started.

NICE suggested that exenatide therapy should only continue if a beneficial metabolic response (at least a 1% HbA_{1c} reduction after six months and at least a 5% reduction in weight at one year) occurs and is maintained.

A more recent draft technology appraisal document from NICE on 'new therapies' broadened the scope for exenatide use alongside MF or SU if BMI was <35, where initiation of insulin would have considerable occupational implications, or where weight loss would benefit other significant comorbidities such as sleep apnoea.² The final version is scheduled for publication at a similar time to this Association

of British Clinical Diabetologists (ABCD) position statement.

The same NICE document offered preliminary recommendations for the use of DPP-4 inhibitors, namely to consider as second-line therapy instead of an SU when blood glucose remains or becomes inadequate (HbA_{1c} ≥6.5%) with MF if:

- The person is at significant risk of hypoglycaemia and its consequences. This may include older people and those in certain occupations (e.g. working at heights or with heavy machinery) or those in certain social circumstances (e.g. living alone).
- The patient does not tolerate an SU (or it is contraindicated).

In addition, DPP-4 inhibitors could be added as second-line therapy to SU monotherapy when blood glucose remains or becomes inadequate (HbA_{1c} ≥6.5%) if:

- The person does not tolerate MF (or it is contraindicated).
- A trial of MF in combination with

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an SU does not adequately control blood glucose ($HbA_{1c} \leq 7.5\%$) and human insulin is unacceptable or inappropriate.

DPP-4 therapy should be continued only if a beneficial metabolic response (at least a 0.7% percentage point HbA_{1c} reduction in six months) occurs and is maintained.

NICE also stated the need to discuss with patients the potential benefits and harms of treatment with a DPP-4 inhibitor to enable an informed decision to be made, and suggested a DPP-4 inhibitor may be preferable to a glitazone for people:

- In whom further weight gain would cause or exacerbate psychological or medical problems associated with a high body weight.
- In whom a glitazone is contraindicated.
- Who have previously had a poor response or were intolerant of glitazone therapy.

The extended options for the treatment of type 2 diabetes and the relatively small evidence base of these new therapies make their placement somewhat challenging. In addition to NICE recommendations, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have recently published a consensus algorithm suggesting a more restricted role for these 'less well validated therapies',³ whereas the Canadian Diabetes Association has suggested an equivalent role as second-line therapy for glucagon-like peptide-1 (GLP-1) analogues and gliptins alongside all other hypoglycaemic agents.⁴

This current position statement from the ABCD summarises our views on current best practice with incretin mimetics and gliptins.

Incretin mimetics

Exenatide

Exenatide, a long-acting incretin mimetic, has been demonstrated to reduce HbA_{1c} by 0.8–1% over six months from an average of 8.2–8.6% with MF and/or SU, associated with weight loss of 0.7–2.5kg, and this was sustained in observational studies with potentially greater weight loss at three years.⁵ Comparison of twice-daily

exenatide with once-weekly exenatide LAR (long-acting-release) over six months in patients on oral hypoglycaemic agents, with an average HbA_{1c} of 8.3% and weight of 102kg, demonstrated a drop in HbA_{1c} of 1.5% and 1.9%, respectively, with similar weight loss of 3.6 *vs* 3.7kg.⁶ In comparison to insulin regimens, weight reduction has been observed with equivalent glycaemic benefit after one year of exenatide, with less hypoglycaemic episodes, but more frequent gastrointestinal side effects.⁷ A more recent six-month study found exenatide to be less efficacious than twice-daily insulin, but patients had an average nine-year duration of diabetes, when a degree of insulin deficiency could have been expected.⁸

The major side effect of exenatide is nausea in up to 50% of cases after initiation of low dose, but after dose titration this usually improves. Importantly, patient drop out through nausea and vomiting was no more than 5–10% in published studies. Hypoglycaemia does not occur more often than with placebo in combination with MF but is more common with an SU, although this is predominantly mild hypoglycaemia. ABCD would recommend dose reduction of an SU on initiation of exenatide in most cases. Recent reports of pancreatitis in 30 patients treated with exenatide predominantly were in cases with gall stones or high alcohol intake. More recently, there has been a further report of six patients with haemorrhagic or necrotising pancreatitis; all were hospitalised and two died. A recent drug safety surveillance system using a health insurance database suggested no excess cases of pancreatitis with either exenatide or sitagliptin.⁹

The ABCD nationwide exenatide audit has to date analysed patient experience in nearly 4000 patients and offers some insight into issues of safety and efficacy.¹⁰ Only one case of pancreatitis in a markedly hypertriglyceridaemic man was reported, with uncertainty over any link with exenatide itself. It is not clear whether exenatide itself could induce pancreatitis in predisposed individuals, but currently ABCD would recommend exenatide should not be initiated in individuals with high alcohol intake or a history of

symptomatic gall stones and in general patients should be warned to stop exenatide if abdominal pain ensues, when appropriate investigations should be initiated. Other patients at risk of pancreatitis, such as those on steroids or with fasting hypertriglyceridaemia $>6\text{mmol/L}$, might best avoid incretin mimetics till more safety data are forthcoming. If exenatide is to be offered in such cases it should only be under specialist supervision with careful monitoring of triglyceride levels in the latter case. Routine ultrasonic assessment for asymptomatic gall stones prior to initiation of exenatide is not currently recommended, not least given the technical difficulties in imaging patients with significant obesity.

Unlicensed use of exenatide alongside insulin has been shown to be effective in a number of reports.¹¹ ABCD is not recommending this practice routinely. However, the nationwide ABCD exenatide audit recorded over 1000 cases on insulin-exenatide combination. Preliminary analyses suggest that withdrawal of insulin when exenatide is commenced as stated in the licensed indication leads to important worsening of glycaemic control, especially in more obese patients with lower HbA_{1c} , implying the benefit of concomitant insulin therapy. The ABCD audit is ongoing and will provide further experience of this combination. ABCD supports a restricted specialist diabetologist role for insulin-exenatide combination therapy in carefully controlled situations where insulin sparing and weight loss in comorbid obesity are demonstrated. We would recommend reduction in dose of insulin of 20–50% on initiation of exenatide in combination with insulin to prevent hypoglycaemia, with careful monitoring to ensure control does not deteriorate.

The ABCD audit recorded that a proportion of very poorly controlled patients may put on weight on exenatide with improved glycaemic control through reduced glycosuric calorie loss. Conversely, the greatest weight loss with exenatide appeared to be in the more obese patients whose HbA_{1c} was initially less elevated.

On initiation of exenatide ABCD would recommend patients should be



fully informed and warned of potential side effects such as abdominal pain, nausea, vomiting and early satiety.

Given the absence of long-term data, ABCD supports a role for exenatide in obese patients (BMI >30) with type 2 diabetes with moderate control on oral agents where insulin might otherwise be considered, and particularly in morbid obesity (BMI >40), where exenatide could be considered as a possible second-line option after MF. In contrast to NICE, we would suggest continuation of exenatide beyond six months if the patient loses 5% of their body weight or HbA_{1c} drops by 1%, or loses 3% of their body weight and HbA_{1c} drops by 0.5%, as cumulative benefit may be observed thereafter. Patient selection could be guided by the experience of the full ABCD audit. Currently, ABCD would also recommend that exenatide is only initiated in PSV-LGV driving licence holders by specialist diabetologists, who are currently responsible for completion of their DVLA reports. An additional area for specialist initiation would be in patients who have undergone or are contemplating bariatric surgery.

For a summary of recommendations see Box 1.

Liraglutide

Liraglutide has been demonstrated to reduce HbA_{1c} by up to 1.1% from a baseline of 8.4% at a 1.8mg single dose in published studies over six to 12 months, and to reduce weight by up to 2.8kg compared with an increase in weight of up to 2.1kg with an SU or glitazone.^{12–14} It appears to have gastrointestinal side effects similar to but less frequent than those of exenatide, and a lower risk of hypoglycaemia. Five patients on liraglutide developed pancreatitis in trials, but causation remains speculative. The development of antibodies following liraglutide is less than with exenatide, but the clinical consequences of this difference are unknown. Although liraglutide has an advantage as a once-daily injection, it is not currently licensed in the USA, where the FDA deferred approval. By contrast, the European Medicines Agency (EMA) has just recommended the licensing of liraglutide.

Box 1. ABCD recommendations for exenatide – 2009

- Consideration in patients with BMI >30 and type 2 diabetes with moderate control on oral agents (HbA_{1c} >7.5%) where insulin might otherwise be indicated
- Particularly consider in morbid obesity (BMI >40) as a possible second-line option after metformin
- *Possible role in combination with insulin in carefully controlled situations especially where insulin sparing and weight loss could benefit comorbidity, e.g. sleep apnoea. Reduction in insulin dose of 20–50% on initiation of exenatide
- Exenatide is not currently recommended to be started in anyone with high alcohol intake or fasting hypertriglyceridaemia >6mmol/L
- *If there is a history of gallstones, exenatide should only be considered in carefully monitored situations and patients should be warned to stop treatment if abdominal pain ensues, when appropriate investigations should be initiated
- Reduction in dose of sulphonylurea of 50% on initiation of exenatide to prevent hypoglycaemia, unless HbA_{1c} >10%.
- Continuation of exenatide beyond six months if the patient loses 5% of their body weight and/or HbA_{1c} drops by 1%, or loses 3% of body weight with a drop of at least 0.5% in HbA_{1c}

*Specialist diabetologist use only.

DPP-4 inhibitors

Clinical trial data for the two licensed DPP-4 inhibitors, sitagliptin and vildagliptin, demonstrate efficacy alongside SU, MF and glitazones, reducing HbA_{1c} by 0.6–1.1% and effectively weight neutral, with potentially less hypoglycaemia and relative weight loss in combination with MF compared to a standard SU/MF combination.^{15,16} Efficacy has been demonstrated for up to a year, and potency is similar to add-on glitazone therapy.

Sitagliptin

Post-marketing surveillance of sitagliptin has recorded several hypersensitivity reactions including Stevens-Johnson syndrome, within the first three months of treatment and sometimes after the first dose. Prescribers should be aware of this and monitor the patients – any hypersensitivity reaction should induce cessation of treatment. Whilst these hypersensitivity reactions were not statistically significant in any of the clinical trials, recent experience with regard to glitazones, bone loss and cardiovascular disease offers pause for thought. A recent report demonstrated rhabdomyolysis in a patient with poor renal function on sitagliptin and high dose simvastatin.¹⁷ ABCD would concur with the *British National*

Formulary advice, and would recommend avoiding gliptins in those with creatinine clearance <50ml/min and close observation with initiation of other potentially nephrotoxic drugs such as NSAIDs.

Vildagliptin

Raised liver enzymes associated with 100mg vildagliptin have led to recommendation for routine monitoring of liver function tests (LFTs) when used at 50mg od with an SU and bd with MF or a glitazone. Whereas vildagliptin should not be prescribed to patients with liver dysfunction and LFTs should be monitored at baseline and every three months for the first year, then annually, there are not stated to be any such restrictions with sitagliptin.

ABCD would currently advise caution with gliptins in cases with hepatic dysfunction at present. The role of these agents with concomitant non-alcoholic fatty liver disease (NAFLD) is yet to be established and it may be that careful selection in future might identify a cohort with NAFLD and type 2 diabetes where a gliptin such as sitagliptin might be a selection of choice. ABCD would recommend either gliptin is withdrawn if a three-fold rise in transaminases from baseline is observed. When a decision is

**Box 2.** ABCD recommendations for gliptins – 2009

- Consideration in patients with type 2 diabetes with moderate control on metformin alone if significant hypoglycaemia with or intolerant of/unsuitable for a sulphonylurea or glitazone
- Consideration in patients with type 2 diabetes with moderate control on metformin and sulphonylurea if glitazone inappropriate
- Avoid gliptins if eGFR <50
- Measure baseline LFTs prior to initiation of vildagliptin; stop if three-fold rise
- Patients on gliptins must be carefully monitored for possible hypersensitivity reactions
- Continuation of gliptin beyond six months if HbA_{1c} drops by at least 0.5%

made to initiate a gliptin we would recommend continuation only if an HbA_{1c} decrease of at least 0.5% occurs at six months.

The potential non-specificity of gliptins on other DPP systems and on other peptides and cytokines is an issue, which ADA-EASD alluded to in respect of immune responsiveness and an increased incidence of upper respiratory tract infections.³ Given the relatively non-specific action of gliptins, long-term adverse effects remain a possibility.

For a summary of recommendations see Box 2.

Conclusion

The potential positives and negatives of all treatment options for patients with type 2 diabetes need to be discussed fully so informed decisions can be made in partnership with each patient. The final placing of incretin mimetics and gliptins cannot be stated with certainty at present and these recommendations are considered preliminary. Given their important benefit in the management of obese type 2 diabetes, these agents should be considered alongside current dietetic and therapeutic weight management strategies. ABCD supports the recommendations of ADA-EASD and NICE in broadly considering MF, SU and insulin as the main therapeutic tools for the majority of type 2 diabetes – with a selected role for incretin mimetics, gliptins and glitazones where issues of obesity, hypoglycaemia and insulin resistance predominate, and where issues of lifestyle and cardiorenal and hepatobiliary status are taken into account. Both GLP-1 analogues and gliptins are contraindicated in women of child-bearing potential.

In patients with significant obesity and suboptimal glycaemic control (HbA_{1c} ≥7.5%) ABCD would consider a role for DPP-4 inhibitor therapy alongside MF, if patients have significant hypoglycaemia with an SU, or as third-line therapy alongside SU/MF especially where glitazones are considered inappropriate.

Exenatide is likely to be a more appropriate option if such treatment is not enabling glycaemic targets to be attained after six months, and/or in more obese/hyperglycaemic cases where insulin therapy may prove counterproductive. The present evidence base suggests that gliptins and incretin mimetics currently have an important restricted role in the management of type 2 diabetes.

Conflict of interest statement

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