NHS Bedfordshire Clinical Commissioning Group

NHS Luton Clinical Commissioning Group

BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE (JPC)

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Bulletin 269: Faster acting insulin aspart (Fiasp®) : New formulation

JPC recommendations:

To support the East of England Priorities Advisory Committee bulletin (version attached).

(This bulletin supersedes previous JPC Bulletin 255)

The East of England
Priorities Advisory Committee
A function of PrescQIPP

GUIDANCE STATEMENT

Faster acting insulin aspart (Fiasp®): New formulation

PAC recommendations

East of England Priorities Advisory Committee recommendations for use in adults and children

1. Faster acting insulin aspart (Fiasp®) is NOT RECOMMENDED for routine prescribing in primary or secondary care.
2. Insulin aspart (Fiasp®) may be of benefit in certain patients with type 1 (T1DM) or type 2 (T2DM) diabetes who fulfil the following criteria, only if first line use of conventional insulin aspart or insulin lispro has been tried and failed:
    - T1DM patients on insulin pumps.
    - T1DM patients on basal bolus insulin needing tight control.
    - In patients where post meal hyperglycaemia could be contributing to sub-optimal control of blood glucose and the patient is experiencing regular post-prandial glucose "spikes" of >8mmol/mol 1 to 3 hours after eating, despite optimisation of all other factors including correction of background or basal insulin, timing of bolus injections, optimised carbohydrate counting, and improved injection technique/site.
    - Pregnant patients (T1DM and T2DM or gestational diabetes mellitus) on insulin. This group typically have a very rapid post-meal blood glucose (BG) rise especially after breakfast with high peaks one hour post-meal, which is not well captured even by conventional aspart (Novorapid®) taken 30 minutes before meal.
3. Faster acting insulin aspart (Fiasp®) should be initiated by a Specialist Diabetes team or Consultant Diabetologist only and is NOT suitable for initiation by GPs or other prescribers in primary care unless under the supervision of a specialist. It is recommended that the initial dose titration and monitoring is closely supervised by a specialist team.
4. Patients should be returned to previous treatment if no improvement in overall disease control including improvement in HbA1c after six months.
5. Ongoing provision of the insulin may be undertaken in primary care by agreement between the specialist and the patient's GP.
6. All insulin aspart formulations including Fiasp® and Novorapid® should be prescribed by brand.
7. These recommendations will be reviewed if and when any new evidence on clinical and cost effectiveness becomes available, or on the launch of insulin aspart biosimilar products or other relevant acting bolus insulins.

Key points

- Insulin aspart is a fast-acting insulin analogue with a short duration of action. It has been licensed in the UK since 1999, as Novorapid®. Faster acting insulin aspart or Fiasp®, is a newly licensed formulation of insulin aspart with a more rapid onset of action than conventional insulin aspart (Novorapid®) and is indicated for the treatment of diabetes mellitus in adults for use at mealtimes, as part of a daily basal-bolus regimen, which also includes an intermediate or longer acting insulin.
- Faster acting insulin aspart (Fiasp®) is administered as a subcutaneous injection and can be injected from two minutes before the start of a meal and up to 20 minutes after starting a meal. It is not licensed in children.
- According to the 2011 International Diabetes Federation (IDF) guideline for management of post-meal glucose in diabetes, hyperglycaemia after meals is associated with an increased risk of micro and macrovascular complications. However, the minimum clinically important difference or target range for postprandial glucose (PPG) is not well defined in T1DM. NICE consider a change of 1mmol/L to be clinically important in T2DM.
- The safety and efficacy of faster acting aspart (Fiasp®) has been investigated in approximately 2,048 patients with either T1DM or T2DM in three phase-3 clinicals trials: onset 1, onset 2 and onset 3.
- The trials reported that faster acting aspart was non-inferior to conventional aspart in onset 1 and 2, while onset 3 found faster acting aspart plus basal insulin to be superior to basal insulin alone. Onset 1 also found that faster acting aspart taken 20 minutes after the start of a meal was non-inferior to conventional aspart taken 0-2 minutes before eating. None of the trials found any difference in effect on mean body weight.
- There is limited long term data beyond 26 weeks' treatment and no data beyond 52 weeks' treatment. Data from a 26-week extension phase to onset 1 suggests that 52-week data indicates that the difference in effect between faster acting aspart and conventional aspart was less pronounced compared to week 26; initial gains in improvement in PPG and HbA1c at 26 weeks were not maintained at 52 weeks. Full details of this extension phase have not been published to date.
- Data from the pivotal onset clinical trials show a clinically relevant but expected glucose lowering effect associated with treatment with faster acting aspart. However, there is no consistent data to support that the small differences in HbA1c documented in patients with T1DM will translate into a reduced risk in diabetic complications. The differences in PPG could possibly be of clinical relevance, but it is uncertain if the effect on PPG is an independent marker of risk considering the limited effect on HbA1c. Data from the extension trial indicates that the effect decreased over time. Overall the clinical data shows that with conventional aspart there is a shift in the pharmacokinetic/ pharmacodynamic (PK/PD) profile resulting in an earlier onset of the glucose lowering effect for faster aspart compared to conventional aspart, while the total glucose-lowering effect is similar. The clinical significance of the PPG findings in onset 1 and the shift to PK/PD profile is unclear.
- There is limited data in patients over the age of 75 years; only 24 patients over the age of 75 were included in the clinical trials. There is no indication the effect is dependent on age. There is limited data available in children. Fiasp® is not currently licensed for use in children and young people under the age of 18 years.
- The efficacy in relation to use in insulin pumps has not be adequately studied more data is required.
- In onset 1 the incidence of severe or plasma glucose-confirmed hypoglycaemia within one hour of administration was significantly higher with mealtime faster acting aspart than conventional aspart (33.9% vs. 28.4%).
- There appears to be no objective evidence currently that faster acting aspart is superior to the other fast acting bolus insulins in specific patient groups such as pregnant women and patients who

experience dawn phenomenon (otherwise known as dawn effect), defined as an abnormal early morning increase in blood glucose - usually between 2am and 8am.

- There was no apparent difference in bolus insulin requirements between faster acting aspart and conventional aspart. The patent for insulin aspart (Novorapid®) expired in 2011, although a formulation patent remained in place for NovoRapid® until June 2017. There are several insulin aspart biosimilars in development, but none have so far progressed beyond phase I trials.
- There is limited cost effectiveness data available. Based on current cost, the cost impact is anticipated to be limited, since the price is the same as Novorapid® and only slightly more than Apidra® (insulin glulisine) and Humalog® (insulin lispro). If Fiasp® is used instead of Novorapid® the cost pressure is currently zero. However, the cost implications will need to be revisited if and when a biosimilar insulin aspart formulation becomes available or the price of Fiasp® increases.
- It is not clear whether the difference in onset of action between faster acting aspart and conventional aspart translates to any important clinical differences, but differences in timing of hypoglycaemia may be clinically important. More data is required.
- The place in therapy of Fiasp® in relation to other bolus insulins remains to be fully determined but can be considered to be similar to conventional aspart and other fast acting insulin analogues, until further evidence or information regarding to superiority, if any, becomes available.
- Despite a lack of robust evidence, local East of England Diabetologists have suggested that faster aspart may be of use in the certain situations as specified in main recommendations box, only if first line use of conventional insulin aspart or insulin lispro has been tried and failed (i.e. faster acting aspart) should only be used second line.
- These recommendations will be reviewed if and when any new evidence on clinical and cost effectiveness becomes available, or on the launch of insulin aspart biosimilar products or other relevant acting bolus insulins.

Proposed sector of prescribing: Primary and secondary care

Introduction

Diabetes mellitus is a group of metabolic disorders in which persistent hyperglycaemia is caused by deficient insulin secretion, or by resistance to the actions of insulin, often combined with relative insulin deficiency. Insulin deficiency and insulin resistance leads to the abnormalities of carbohydrate, fat, and protein metabolism that are characteristic of diabetes mellitus.[1-3] Subcutaneous insulin is used in T1DM and T2DM to control blood sugar and symptoms.

The National Institute for Health and Care Excellence (NICE) currently recommends a basal-bolus insulin regimen in T1DM.[4] This involves using longer acting insulin (basal or background insulin) to keep blood glucose levels stable through periods of fasting and separate injections of shorter acting insulin (bolus), such as neutral or soluble insulin (Actrapid®, Humulin S®), to prevent rises in blood glucose levels resulting from meals.

Chronic hyperglycaemia defines diabetes, and glycaemic control is fundamental to diabetes management. Improvement in long-term glucose control has been demonstrated to reduce the incidence and progression of complications in people with T1DM and T2DM.[5] Both fasting glycaemia and glycaemic excursions occurring after meals contribute to overall glycaemic burden, a major contributor to the microvascular and macrovascular complications of diabetes. Control of glycaemic excursions after meals contributes to lowering of the glycosylated haemoglobin (HbA1c) level. As HbA1c decreases, the relative contribution of post-meal glucose control on HbA1c levels increases. According to the 2011 International Diabetes Federation (IDF) guideline for management of post-meal glucose in diabetes, hyperglycaemia after meals is associated with an increased risk of micro and macrovascular complications.[6]

Insulin aspart is a fast-acting insulin analogue with a short duration of action. It has been licensed in the

UK since 1999, as Novorapid®.[7,8] Fiasp® is a newly licensed formulation of insulin aspart with a more rapid onset of action than Novorapid®.[7,9] The active substance, insulin aspart, is identical to Novorapid®, however nicotinamide (vitamin B3) and the amino acid, L-arginine, have been added to the formulation as excipients. The marketing authorisation holder, Novo Nordisk, states that this results in a faster onset of action, due to a reduction in the occurrence of self-association of insulin aspart.[9] Self-association of the insulin molecule results in decreased and slower absorption of insulin and a delayed onset of action.[10]

Fiasp® is indicated for the treatment of diabetes mellitus in adults and is intended for use at mealtimes, as part of a daily basal-bolus regimen, which also includes an intermediate or longer acting insulin. Fiasp® is administered as a subcutaneous injection and can be administered from two minutes before to up to 20 minutes after starting a meal.[9]

Current alternative fast acting insulin analogues include insulin lispro (Humalog®) and insulin glulisine (Apidra®) however, other faster acting or "ultrafast"-acting insulins are in development, including Ultra-Rapid BioChaperone Lispro (Adocia®), a newly formulated version of insulin lispro.[11]

See appendix 1 for comparative information in relation to pharmacokinetic parameters of the various available insulins.

Evidence

The safety and efficacy of faster acting aspart (Fiasp®) has been investigated in three main phase-3 clinical trials; onset 1, onset 2 and onset 3.[12-14] The primary efficacy endpoint in each trial was change in HbA1c from baseline to end of treatment.

Onset 1 was a 26-week double-blind non-inferiority trial, involving 1,143 adult patients with T1DM. After an eight week run in phase, subjects were randomised 1:1:1, to either double blind mealtime faster aspart (n=381); conventional insulin aspart (IAsp, n=380) administered 0-2 minutes before the start of meals, or open label post meal faster aspart (n=382). Insulin determir was administered as the background basal insulin. At 26 weeks, the estimated treatment difference (ETD) between mealtime faster aspart and conventional IAsp was -0.15% [95% CI -0.23; -0.07] or -1.62mmol/mol [-2.50; -0.73] vs. the post meal faster aspart group; ETD 0.04% [-0.04; 0.12] or 0.47mmol/mol [-0.41; 1.36]; p<0.0001 for non-inferiority. The study authors reported that non-inferiority for faster aspart versus conventional IAsp had been demonstrated.[12]

Secondary endpoints for onset 1 included change in baseline in 2 hourly post prandial glucose increments (meal test). At study end, postprandial plasma glucose (PPG) increments were statistically significantly lower with mealtime faster aspart at 1 hour (ETD −1.18 mmol/L [95% CI −1.65; −0.71], −21.21 mg/dL [−29.65; −12.77]; p<0.0001) and at 2 hours (−0.67 mmol/L [−1.29; −0.04], −12.01 mg/dL [−23.33; −0.70]; p=0.0375) after the meal test and the study authors reported that superiority to IAsp was confirmed.

In onset 2, also a 26-week double-blind non-inferiority trial, 689 adult patients with T2DM on oral antidiabetic medication and baseline HbA1c of between 7.0-9.5%, received either faster aspart (n=345) or IAsp (n=344). Both were administered 0-2 minutes before the start of meals. After 26 weeks, change in HbA1c was -1.38% with faster aspart and -1.36% with IAsp; mean HbA1c was 6.6% in both groups. The ETD was reported as -0.02% [-0.15; 0.10]. The study authors concluded that non-inferiority between treatments had been demonstrated.[13]

Both treatments improved postprandial plasma glucose (PPG) control. The estimated change from baseline in 1 hour PPG increments was -2.1 mmol/L (-38.5 mg/dL) for faster aspart and -1.6 mmol/L (-27.9 mg/dL) for IAsp. The ETD was -0.59 mmol/L [95% CI -1.09; -0.09]; -10.63 mg/dL [-19.56; -1.69]), which was statistically in favour of faster aspart (p=0.0198). Statistical superiority of treatment with faster aspart versus IAsp could not be confirmed for the change from baseline in 2 hour PPG increments. Estimated change from baseline in 2 hour PPG increments was -3.2 mmol/L (−58.3 mg/dL) with faster aspart versus −2.9 mmol/L (−51.8 mg/dL) for IAsp. The ETD was -0.36 mmol/L [95% CI −0.81; 0.08] -6.57 mg/dL [-14.54; 1.41], which did not reach statistical significance. There were no statistical differences

between groups for change from baseline in 3 hourly or 4 hourly PPG increments or in PPG at any time point. The study authors reported that faster aspart improved hourly PPG with no differences in 2-4 hourly PPG versus IAsp.[13]

Onset 3, an 18-week open-label, randomised, superiority trial involving 236 adult patients with inadequately controlled T2DM, compared faster aspart plus basal insulin (basal-bolus (BB) group) to basal insulin alone. Both groups were also taking metformin. After 18 weeks, HbA1c decreased from 7.9% (63.2mmol/mol) to 6.8% (50.7mmol/mol) in the BB group versus 7.9% (63.2 mmol/mol) to 7.7% (60.7mmol/l) in the basal insulin only group, the ETD was −0.94% [95% CI −1.17; −0.72]; −10.3 mmol/mol [−12.8; −7.8]; p<0.0001. Reductions from baseline in overall mean 2 hour PPG and overall PPG increment for all meals (self-measured plasma glucose profiles) were statistically significant in favour of BB treatment (p<0.0001).[14] The study authors reported that faster aspart in a BB regimen provided superior glycaemic control as compared with basal insulin alone. It should be noted however that treatment with conventional aspart was not included in this trial and therefore no direct comparison to current available alternative bolus insulin was made by this particular trial.

Long term data

Onset 1 also had a 26-week extension phase, for a total of 52 weeks' treatment. The full 52-week group included 381 participants who received faster aspart and 380 participants who received IAsp. At study end, estimated mean changes from baseline in HbA1c levels were -0.08% in the faster aspart group and +0.01% in the IAsp, estimated treatment difference -0.10%, [95% CI -0.19 to 0.00] with borderline statistical significance. HbA1c increased again after the initial decline during the first 26 weeks of treatment and the difference between treatment groups was smaller at 52 weeks, than after 26 weeks in both treatment groups. No difference in the HbA1c responder endpoints was observed between mealtime faster aspart and conventional IAsp. The estimated treatment differences for PPG at 1 and 2 hours after start of the meal test only reached statistical significance at 1 hour. Changes from baseline in 1 hour post prandial plasma glucose increment (meal test) were faster aspart -1.05mmol/L versus IAsp -0.14mmol/L. ETD -0.91mmol/L [95% CI -1.40, -0.43] or -16.48mg/dL [95% CI -25.17; 7.80], p=0.002.[15]

Insulin pumps: One very small study has assessed the use of faster aspart in subcutaneous insulin pumps.[16]

In a randomised, double blind, crossover, active controlled trial, 2 hour post prandial plasma response was compared in 43 adult patients with T1DM following two weeks' treatment with faster aspart and IAsp.[16] The primary endpoint was mean change in PPG 2 hours after a standardised meal test. All subjects had masked continuous glucose monitoring (CGM) throughout. Insulin dose adjustments were made based on masked CGM data during contact with the investigator. The basal rate of infusion, insulin to carbohydrate ratio (ICR) and insulin sensitivity factor (ISF) were established in the first week of each treatment period. Each bolus dose was established by the subject using the pump bolus calculator (under supervision of the investigator). The study authors reported that after two weeks of treatment with each insulin, faster aspart produced a greater glucose lowering effect than conventional aspart, during the 2 hours post administration of the standardised meal test [PPG average,0–2h: 3.03mmol/L versus 4.02mmol/L (54.68mg/dL vs. 72.52mg/dL); ETD -0.99mmol/L [95% CI; −1.95; -0.03]; -17.84mg/dL [−35.21; -0.46]; p=0.044. One hour post meal, PPG levels were -1.64mmol/L (-29.47mg/dL) lower with faster aspart versus IAsp (p=0.006). Interstitial glucose (IG) profiles supported these findings; the largest differences were observed at breakfast but were not statistically significant: 9.08 versus 9.56mmol/L (163.57 vs. 172.19 mg/dL; ETD -0.48mmol/L [−0.97; 0.01]; -8.62 mg/dL [−17.49; 0.24]; p=0.057). Duration of hypoglycaemia (described as low IG levels by study authors, 3.9mmol/L [70mg/dL] per 24 h), was statistically significantly shorter for faster aspart versus IAsp (2.03 h vs. 2.45 h; ETD -0.42 [−0.72; -0.11]; p=0.008). The daily bolus, basal and total doses of insulin and insulin delivery parameters were similar between both faster aspart and conventional IAsp groups. The clinical significance of these findings is unclear, and more data is required to confirm place in therapy of faster aspart in relation to insulin pumps.

A second, randomised, double blind, parallel group, active controlled trial, has assessed the pump compatibility of faster aspart in 37 adult patients with T1DM.[17] The primary endpoint was the number of microscopically confirmed episodes of infusion set occlusions. Efficacy and safety measures were included as secondary endpoints. Following a run-in phase, subjects were randomised (2:1) to faster aspart (n=25) or insulin aspart (n=12) for six weeks. No microscopically confirmed episodes of infusion set occlusions were observed in either treatment arm. Seven possible infusion set occlusions were reported by five subjects, all in the faster aspart group, however none were confirmed. The study authors reported a non-significant trend toward better efficacy in the faster aspart group: ETD in HbA1c change -0.14% [-0.40, 0.11]. No new safety issues were found in either treatment group.

Children

Faster aspart (Fiasp®) is not currently licensed for use in children and young people under the age of 18 years, as there is limited evidence available.[9] A small randomised double-blind, pharmacokinetic trial involving 12 children (aged 6-11 years) and 13 adolescents (12 -17 years) with T1DM compared the onset of action between faster aspart vs. conventional insulin aspart. Subjects received 0.2 U/kg subcutaneous dosing (mean of 8.3, 12.8, and 15.6 U, respectively) immediately prior to a standardised meal (17.3 g carbohydrate/100 mL; amount adjusted by body weight). Consistently across age groups, onset of effect occurred approximately twice-as-fast (5-7 minutes earlier) and early exposure defined as area under the IAsp curve from 0 to 30 minutes (AUC IAsp,0-30min) was greater (by 78%-147%) for faster aspart vs. IAsp, with no treatment differences in total exposure (AUC IAsp,0-t) or maximum concentration (Cmax). Two-hour post meal plasma glucose excursion was reduced for faster aspart vs. IAsp.[18]

Adverse events

The safety profile of faster aspart (Fiasp®) was assessed in 1,244 patients exposed to faster aspart and 853 who received comparators, mainly in onset 1 and 2.[5,12,13]

There were no clinically important differences reported in the rate of overall adverse events (AEs) or serious AEs reported between faster aspart and IAsp. The overall rate of AEs was higher in patients with T1DM (73%) than T2DM (53%), but there was no difference between faster aspart and IAsp. Almost all patients (>90%) experienced at least one hypoglycaemic event, although most were mild or moderate and hypoglycaemia was more common in patients with T1DM irrespective of treatment allocation.[5]
In onset 1, the incidence of severe or plasma glucose-confirmed hypoglycaemia within one hour of administration was significantly higher with mealtime faster aspart than IAsp (33.9% vs. 28.4%).[5,12] There was no significant overall difference between post-meal faster aspart and IAsp. Severe or confirmed hypoglycaemia within 2 hours following a meal was more common with faster aspart (32.8% vs. 28.2%, rate ratio 1.60, 95% CI 1.13 to 2.27, p=0.008). There was no difference between treatment groups in mean rates of hypoglycaemia over longer periods post administration (2-24 hours). There was a similar pattern of hypoglycaemia in onset 2.[5,13]

The European Medicines Agency (EMA), noted a statistically significant difference in the rate of mealtime hypoglycaemic episodes one hour after a meal in T1DM and 2 hours after a meal in T2DM. Higher rates were seen in the faster aspart mealtime group compared to the group using IAsp and reflects the pharmacodynamic-pharmacokinetic (PD/PK) findings, with faster action of faster aspart compared to IAsp and supports a significant difference of the safety profile between the two formulations.[5] Further data is required to confirm clinical significance.

No differences in development of insulin antibodies were detected between the two formulations.[5]
Injection site reactions were slightly more common with faster aspart than with conventional IAsp; 3.8 events vs. 2.4 events per 100 patient-years of exposure, no statistics presented. However, the committee on medicinal products for human use (CHMP), considers that if the study group is limited to T1DM, a clinically relevant increase in the frequency of injection site reactions occurred, (4.8 and 5.5 per 100 patient years of exposure [PYE] in the mealtime and post meal faster aspart groups) compared to IAsp (1.6 per 100 PYE).

All suspected adverse reactions to black triangle drugs, such as faster aspart (Fiasp®) should be reported to the MHRA via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

Evidence strengths and limitations

- Faster aspart (Fiasp®) has been shown to be non-inferior to conventional aspart (Novorapid®).
- There is limited long term data beyond 26 weeks' treatment and no data beyond 52 weeks' treatment. Initial gains in improvement in PPG and HbA1c at 26 weeks were not maintained at 52 weeks.
- There is limited data in patients over the age of 75 years; only 24 patients in the clinical trials. However, there is no indication the effect is dependent on age.
- The efficacy in relation to use in insulin pumps has not be adequately studied and more data is required.
- There is little data in available in children. Fiasp® in not currently licensed for use in children.
- The data from the pivotal clinical trials show a clinically relevant glucose lowering effect associated with treatment with faster aspart which is to be expected as the active component is insulin aspart. However, there is no consistent data to support that the small differences in HbA1c documented in patients with T1DM would translate into a reduced risk of diabetic complications. The differences in PPG could possibly be of clinical relevance, but it is uncertain if the effect on PPG is an independent marker of risk considering the limited effect on HbA1c. Further, from data in the extension trial, the effect decreased over time.
- The clinical significance of the PPG findings in onset 1 is therefore unclear. According to the 2011 International Diabetes Federation (IDF) guideline for management of post-meal glucose in diabetes, hyperglycaemia after meals is associated with an increased risk of micro and macrovascular complications. However, the minimum clinically important difference or target range for postprandial glucose (PPG) is not well defined in T1DM. NICE consider a change of 1 mmol/L to be clinically important in T2DM.
- The data available with respect to faster aspart shows that, compared to conventional IAsp (NovoRapid®), there is a shift in the PK/PD profile resulting in an earlier onset of the glucose-lowering effect while the total glucose-lowering effect is similar. The clinical significance of this is unclear.
- There appears to be no objective evidence currently that faster aspart is superior to the other fast acting bolus insulins in specific patient groups such as pregnant women, and patients who experience dawn phenomenon (otherwise known as dawn effect), defined as an abnormal early morning increase in blood glucose - usually between 2am and 8am.

Current guidance and implementation considerations.

There is no specific recommendation from NICE regarding faster acting insulin analogues as yet.[1,4,19-21]

For adults with T1DM, NICE recommends offering rapid-acting insulin analogues to be injected before meals, in combination with a basal insulin. People with a strong preference for an alternative mealtime insulin should be offered their preferred choice.[19,20] Patients should not be advised to take rapid-acting insulin analogues after meals (NICE "Do Not Do" recommendation).[21]

For adults with T2DM who require insulin, the first-line choice is NPH insulin injected once or twice daily according to need.[19] A short-acting insulin should be considered alongside NPH insulin in people with an HbA1c of 75 mmol/mol (9.0%) or higher. Short-acting insulin analogues in pre-mixed formulations should be considered in preference to human insulins for people who prefer injecting insulin immediately before a meal, when hypoglycaemia is a problem, or if blood glucose levels rise markedly after meals. Short-acting insulins are recommended for use before meals.[20]

The Scottish Medicines Consortium (SMC) has accepted faster aspart (Fiasp®) for use within NHS Scotland.[22] The All Wales Medicines Strategy Group (AWSMG) has excluded Fiasp® from its assessment programme.[23] Formulations are excluded for consideration by AWSMG if certain circumstances apply, including where the product is a new formulation or combination of an established medicine which is an alternative formulation of an established medicine which costs the same or less than the existing established medicine. Full details are available on the AWMSG website.

All insulins should be prescribed by brand.

Comparative costs (eMIMs) and eBNF

Comparative costs between fast acting bolus insulin analogues are shown in Table 1 below.[7,24] Faster acting aspart is included in the NHS National Tariff.[25]

Table 1: Comparative costs of fast acting bolus insulin analogues

Insulin^	Cost per 3mL pen	Cost per unit	Cost per day*	Cost per 28 days	Cost per patient per year
Insulin aspart - Fiasp®	£6.12	£0.0204	£1.1424	£31.9872	£415.83
Insulin aspart - Novorapid®	£6.12	£0.0204	£1.1424	£31.9872	£415.83
Insulin glulisine - Apidra®	£5.66	£0.0189	£1.0565	£29.5829	£384.58
Insulin lispro - Humalog®	£5.89	£0.0196	£1.0995	£30.7851	£400.21

^Insulin strength 100units/ml

*Based on total daily dose for bolus insulin of 0.8units/kg and 70kg patient

There was no apparent difference in bolus insulin requirements between faster aspart (Fiasp®) and conventional aspart (NovoRapid®).[5] The patent for conventional insulin aspart (Novorapid®) expired in 2011, although a formulation patent remained in place for NovoRapid® until June 2017.[11] There are several insulin aspart biosimilars in development, but none have so far progressed beyond phase I trials.[11]

There is limited cost effectiveness data available. A cost utility analysis, based on data from the 26-week main phase of onset 1, has projected that faster aspart could be associated with improved discounted quality adjusted life expectancy (by 0.13 quality adjusted life years versus conventional IAsp).[26] Improved clinical outcomes were assumed to result from fewer diabetes related complications and a delayed time to their onset with faster aspart. The analysis authors also suggested that faster aspart could be associated with reduced costs vs. conventional insulin aspart. Evaluation of direct costs suggested that the mean cost per patient receiving faster aspart was £1,715 lower than in the conventional IAsp arm, over a patient lifetime. The analysis authors also stated that faster aspart was associated with reduced treatment costs, due to lower doses of basal and bolus insulins, with a mean cost saving of £478 patients. However full details of the costings were not included, and onset 1 showed that bolus insulin requirements were comparable between faster acting aspart and conventional aspart at week 26. Data from the onset 1 extension study was not included. More cost effectiveness data is required.

Based on current cost, the cost impact is anticipated to be limited, since the price is the same as Novorapid® and only slightly more than Apidra® (insulin glulisine) and Humalog® (insulin lispro) (i.e. faster aspart is currently cost neutral). However, the cost implications will need to be revisited, if and when a biosimilar insulin aspart formulation becomes available or the price of faster aspart (Fiasp®) increases.

Place in therapy

There are no apparent clinically significant differences between faster aspart (Fiasp®) and conventional aspart (NovoRapid®) and neither drug appears to have a significant clinical advantage.[27]

It is not clear whether the difference in onset of action between faster aspart and IAsp translates to any important clinical differences, however differences in timing of hypoglycaemia may be clinically

important.[27] Faster aspart is licensed for use up to 20 minutes after starting a meal, which may be useful for patients who require additional flexibility around timing of mealtime insulin. However, most patients should be able to inject 20 minutes before a meal, in accordance with current NICE recommendations using a conventional bolus insulin or bolus insulin analogue. More data is required.

The place in therapy of Fiasp® in relation to other bolus insulins remains to be fully determined but can be considered to be similar to conventional aspart (Novorapid®) and other fast acting insulin analogues. Faster aspart (Fiasp®) represents an additional option for certain patients with diabetes who require an ultra-rapid-acting bolus insulin analogue, due to post prandial spikes in blood glucose, which could be contributing to overall hyperglycaemia.[27]

Despite the lack of convincing evidence, local East of England Diabetologists, have suggested that faster aspart could be used in the following situations, and only if first line use of conventional insulin aspart or insulin lispro has been tried and failed (i.e. Fiasp® should only be used second line), in the following patient groups:

- T1DM patients on continuous subcutaneous insulin infusion (CSII) pump.
- T1DM patients on basal bolus insulin needing tight control.
- In patients where post meal hyperglycaemia could be contributing to sub-optimal control of blood glucose and the patient is experiencing regular post-prandial glucose “spikes” of >8mmol/mol 1 to 3 hours after eating despite optimisation of all other factors including correction of back ground or basal insulin, timing of bolus injections, optimised carbohydrate counting, and improved injection technique/ site.
- Pregnant women (with T1DM and T2DM or gestational DM) on insulin. This group typically have very rapid post-meal BG rise especially after breakfast with high peaks 1hr post-meal, which is not well captured even by Novorapid taken 30 minutes before meal.

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Document history

PAC approval date	12th March 2018	**Version**	1
Consultation process	PAC members EoE clinicians		
QA process	Katie Smith, Senior Clinical Pharmacist, PrescQIPP. 28th April 2018		
Search strategy	The following databases were searched: NHS Evidence, Embase, Medline including Pubmed, Biomed Central, Medscape, Clinical Key and Cochrane Search terms used were Fiasp, fast* aspart, Novorapid, and aspart; alone and in combination. No limits		

*Consult Summary of Prescribing Characteristics for full prescribing details and upto date guidance in relation to dosing and prescribing recommendations

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

References

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Appendix 1

Comparative pharmacokinetics of insulins

Insulin type	Brand name	Generic name	Onset	Peak	Duration
Bolus insulin	Actrapid®	Soluble or neutral insulin	<30min	1.5-3.5	7-8hr
	Humulin S®	Soluble or neutral insulin	30min-1hr	1-6hr	6-12hr
	Insuman Rapid®	Soluble or neutral insulin	<30min	1-4hr	7-9h
Rapid acting bolus insulin	Novorapid®	Insulin aspart	10-20min	1-3hr	3-5hr
	Humalog®	Insulin lispro	15min	1.5hr	2-5hr
	Fiasp®	Insulin aspart	4min	1-3hr	3-5hr
	Apidra®	Insulin glulisine	10-20 min	55 min	1.5-4hr
Basal insulin	Humulin I®	Isophane insulin (NPH insulin)	30min-1hr	1-8hr	22hr
	Insulatard®	Isophane insulin (NPH insulin)	<1.5hr	4-12hr	24hr
	Insuman Basal®	Isophane insulin (NPH insulin)	<1hr	3-4hr	11-20hr
Basal insulin analogues	Lantus®	Insulin glargine U100	1-4hr	-	24hr
	Abasaglar®	Insulin glargine - biosimilar U100	1-4hr	-	24hr
	Levemir®	Insulin determir	30min-1hr	-	24hr
Basal ultra long acting insulin analogues	Tresiba®	Insulin degludec U100	1-2hr	-	>42hr
High strength basal insulin (concentrated)	Toujeo®	Insulin glargine U300	1-6hr	-	24-36hr
	Tresiba®	Insulin degludec U200	1-2hr	-	>42hr
	Humulin R® (Imported from US - unlicensed in UK)	Insulin human injection, USP	30-45mins	4-8hr	12-24hr

Insulin type	Brand name	Generic name	Onset	Peak	Duration
Biphasic or premixed insulins	Humulin® M3 70/30	Insulin NPH + neutral insulin	30min-1hr	1-12hr	22hr
	Humalog® Mix	Insulin lispro + insulin lispro protamine	15min	2hr	22hr
	Novomix®	Insulin aspart + insulin aspart protamine	10-20 min	1-4hr	24hr
	Insuman® Comb	Neutral insulin + isophane insulin	30min-1hr	2-4hr	11-20hr

Appendix 2: Assessment against Ethical and Commissioning Principles

Treatment assessed: Faster acting insulin aspart (Fiasp®)

East of England Priorities Advisory Committee Recommendation

Not for routine prescribing in primary or secondary care.

Insulin aspart (Fiasp®) may be of benefit in certain patients with type 1 (T1DM) or type 2 (T2DM) diabetes who fulfil the following criteria, only if first line use of conventional insulin aspart or insulin lispro has been tried and failed:

- T1DM patients on insulin pumps.
- T1DM diabetes patients on basal bolus insulin needing tight control.
- In patients where post meal hyperglycaemia could be contributing to sub-optimal control of blood glucose (BG) and the patient is experiencing regular post-prandial glucose “spikes” of >8mmol/mol 1 to 3 hours after eating despite optimisation of all other factors including correction of back ground or basal insulin, timing of bolus injections, optimised carbohydrate counting, and improved injection technique/site.

Pregnant patients (T1DM and T2DM or gestational diabetes mellitus) on insulin. This group typically they have a very rapid post-meal BG rise especially after breakfast with high peaks 1 hour post-meal, that is not well captured even by conventional aspart (Novorapid®) taken 30 minutes before a meal.

Clinical effectiveness

The safety and efficacy of faster acting aspart (Fiasp®) has been investigated in three main phase-3 clinical trials, onset 1, onset 2 and onset 3. The primary efficacy outcome in each trial was change in HbA1c from baseline to end of treatment.

In summary, the results of the onset clinical trial programme reported that faster acting aspart was non-inferior to conventional aspart in onset 1 and 2, while onset 3 found faster acting aspart plus basal insulin to be superior to basal insulin alone. Onset 1 also found that faster acting aspart taken 20 minutes after the start of a meal was non-inferior to conventional aspart taken 0-2 minutes before eating. None of the trials found any difference in effect on mean body weight.

Data from the long-term extension of the onset 1 trial show that in both treatment groups, HbA1c increased again after the initial decline during the first 26 weeks of treatment and the difference between treatment groups was smaller than after 26 weeks. The efficacy in relation to use in insulin pumps has not be adequately studied and more data is required. There is little data available on the use in children. Faster acting aspart (Fiasp®) in not currently licensed for use in children.

Cost effectiveness

There is limited cost effectiveness data available. A cost utility analysis, based on data from the 26-week main phased of onset 1, has projected that faster aspart could be associated with improved discounted quality adjusted life expectancy (by 0.13 quality adjusted life years) versus conventional aspart. Improved

clinical outcomes were assumed to result from fewer diabetes related complications and a delayed time to their onset with faster aspart. The analysis authors also suggested that faster aspart could be associated with reduced costs vs. insulin aspart. Evaluation of direct costs suggested that the mean cost per patient receiving faster aspart was £1,715 lower than in the conventional aspart arm, over a patient lifetime. The analysis authors also stated that faster aspart was associated with reduced treatment costs, due to lower doses of basal and bolus insulins, with a mean cost saving of £478 patients. However, full details of the costings were not included, and onset 1 showed than bolus insulin requirements were comparable between faster acting aspart and conventional aspart at week 26. In addition, it should be noted that the data included was limited to the first 26 weeks of treatment and did not include the data from the extension phase up to 52 weeks, which appears to show a reduction in treatment difference over time. More cost effectiveness data is required.

Based on current cost, the cost impact is anticipated to be limited, since the price is the same as conventional aspart and only slightly more than insulin glulisine (Apidra®) and insulin lispro (Humalog®). If Fiasp® is used instead of conventional aspart the cost pressure is currently zero. However, the cost implications will need to be revisited, if and when a biosimilar insulin aspart formulation becomes available or the price of Fiasp® increases.

Equity

No issues identified.

Health impact Assessment 1: needs of the community

Based on current equal costs of Fiasp® compared to conventional aspart, the likely impact on the community is low and implementation is unlikely to represent a significant cost pressure based on current prices.

It is not clear whether the difference in onset of action between faster aspart (Fiasp®) and conventional aspart, translates to any important clinical differences, more data is required.

The place in therapy of in relation to other bolus insulins remains to be fully determined, but can be considered to be similar to conventional aspart and other fast acting insulin analogues, until further evidence or information regarding to superiority, if any, becomes available.

Health impact assessment 2: need for healthcare (incorporates patient choice and exceptional need)

Faster acting aspart (Fiasp®) represents an additional option for people with diabetes who require a rapid-acting bolus insulin analogue. It is licensed for use up to 20 minutes after starting a meal, which may be useful for patients who require additional flexibility around timing of mealtime insulin. However, most patients should be able to inject 20 minutes before a meal, in accordance with current NICE recommendations using a conventional bolus insulin or bolus insulin analogue. The number of likely patients is unknown, however several alternative effective options to Fiasp® are available which should meet the majority of patient's needs.

Policy drivers

None

Disinvestment

None identified.