New Medicine Recommendation

Insulin Aspart (Fiasp®▼) solution for injection for the treatment of diabetes mellitus in adults

Recommendation: Green (Restricted)

Conditions: Insulin Aspart (Fiasp®) is recommended for the treatment of diabetes mellitus in adults who are suitable for NovoRapid® and their diabetes cannot be adequately managed with alternative formulary choices and at least one of the following applies:

- **Where the prescriber believes a faster onset of action would be beneficial to the patient**
- **Where a patient requires 'tight' control of blood sugar levels**
- **Where a patient has rapid post meal increase in blood sugar levels**

Summary of supporting evidence:

- Fiasp® is insulin aspart in a new formulation with a faster onset of action than NovoRapid®. There are currently no alternative formulations of insulin aspart available or in development.
- **Onset 1** demonstrated noninferiority of Fiasp®, for both mealtime and post-meal dosing, compared to mealtime NovoRapid® in terms of change from baseline in HbA_{1c} in type 1 patients (and superiority for mealtime Fiasp® versus mealtime NovoRapid®).
- **Onset 2** supported the results of **onset 1** demonstrating noninferiority of mealtime Fiasp® with mealtime NovoRapid® in terms of change from baseline in HbA_{1c}.
- Noninferiority of post-meal Fiasp® compared to mealtime NovoRapid® may offer flexibility of bolus dosing in certain situations when an individual is unable to predict the exact timing or carbohydrate content of a meal in advance (e.g. on social occasions), when experiencing lack of appetite or nausea (e.g. the very elderly or frail), when appetite is unpredictable (e.g. children), if an injection is forgotten, or if an individual is anxious about severe hypoglycaemia. [1]
- NICE guidance does not recommend the routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes. [2]
- Apart from differences in the timing of the hypoglycaemic episodes, no significant differences of clinical importance in the pattern, proportions and rates of adverse events were identified between Fiasp® and NovoRapid® in either type 1 or type 2 diabetes mellitus.
- Both **onset 1** and **onset 2** demonstrated superior post prandial glucose control at 1 hour for mealtime Fiasp® compared to mealtime NovoRapid®. The clinical relevance of these findings is uncertain but may benefit certain patient cohorts (e.g. pregnant patients).
- If Fiasp® was used in place of NovoRapid® no cost burden is expected, although availability of Fiasp® could further complicate the treatment pathway given that several rapid-acting insulin analogues are already available.

Details of Review

Name of medicine (generic & brand name)**:** Insulin Aspart (Fiasp®)

Strength(s) and form(s): 100 units/mL solution for injection in pre-filled pen, cartridge or vial [3]

Dose and administration: Dosing is individual and determined in accordance with the needs of the patient.
Fiasp is administered as a subcutaneous injection up to 2 minutes before the start of the meal, with the option to administer up to 20 minutes after starting the meal. [3]

BNF therapeutic class / mode of action:
Insulins and anti-diabetic drugs/ rapid acting insulin

Licensed indication(s):
Treatment of diabetes mellitus in adults

Proposed use (if different from, or in addition to, licensed indication above):
As per licensed indication

Course and cost:
5 x 3mL penfill cartridges- £28.31
5 x 3mL FlexTouch pre-filled pen- £30.60
1 x 10mL vial- £14.01

Current standard of care/comparator therapies:

- NovoRapid® (insulin aspart)
- Apidra® (insulin glulisine)
- Humalog® (insulin lispro)

Relevant NICE guidance:

NICE clinical guideline NG17 (Type 1 diabetes in adults: diagnosis and management) August 2015 indicates that multiple daily injection basal-bolus insulin regimens should be the treatment of choice in all adults with type 1 diabetes in preference to non- basal-bolus insulin regimens (i.e. twice daily mixed, basal only or bolus only regimens). [2]
For rapid-acting insulin NG17 states:

> 1.7.7 Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes.
>
> 1.7.8 Do not advise routine use of rapid-acting insulin analogues after meals for adults with type 1 diabetes.
>
> 1.7.9 If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin.

NICE guideline NG28 (Type 2 diabetes in adults: management) July 2015 advises insulin-based treatment as an option if:

- Dual therapy with metformin and another oral drug has not continued to control $HbA1_c$ to below the patient's individually agreed threshold for intensification or
- Metformin is contraindicated or not tolerated and dual therapy with two oral drugs has not continued to control $HbA1_c$ to below the patient's individually agreed threshold for intensification. [4]

Initially adult type 2 diabetic patients can be offered:

- NPH (isophane) insulin injected once or twice daily.
- Both NPH and short-acting insulin (particularly if the person's HbA1c is 75 mmol/mol [9.0%] or higher), administered either:
  - separately **or**

- as a pre-mixed (biphasic) human insulin preparation.

NG28 also states:

> 1.6.36 Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation).
>
> 1.6.37 Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate.

Background and context

The World Health Organisation defines diabetes as a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels. [5]

Type 1 diabetes affects over 370,000 adults in the UK. Loss of insulin secretion results in high blood glucose and other metabolic and haematological abnormalities, which have both short-term and long-term adverse effects on health. Over years, type 1 diabetes causes tissue damage which, if not detected and managed early, can result in blindness, kidney failure and foot ulceration leading to amputation, as well as premature heart disease, stroke and death. The risk of all of these complications is greatly reduced by treatment that keeps circulating glucose levels to as near normal as possible, reducing tissue damage. Complications can often be prevented by early detection and active management. [2]

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance and insufficient pancreatic insulin production, resulting in hyperglycaemia. Type 2 diabetes is commonly associated with obesity, physical inactivity, raised blood pressure, disturbed blood lipid levels and a tendency to develop thrombosis, and therefore is recognised to have an increased cardiovascular risk. It is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy.

In 2013, over 3.2 million adults were diagnosed with diabetes, with prevalence rates of 6% and 6.7% in England and Wales respectively. It is estimated that about 90% of adults currently diagnosed with diabetes have type 2 diabetes. Type 2 diabetes is more common in people of African, African-Caribbean and South Asian family origin. It can occur in all age groups and is increasingly being diagnosed in children. [4]

Fiasp® is insulin aspart in a new formulation. Compared to NovoRapid® (first marketed insulin aspart formulation), Fiasp® contains two additional excipients: nicotinamide (also known as niacinamide or vitamin B3) and L-arginine hydrochloride (an amino acid). The addition of nicotinamide is intended to result in a faster initial absorption of insulin aspart following subcutaneous (s.c.) injection. The addition of L-arginine hydrochloride should support stabilisation of the Fiasp® formulation.

Fiasp® is intended to be used for the treatment of patients with diabetes mellitus (type 1 and type 2) both for basal-bolus therapy in combination with intermediate- or long-acting basal insulin (± oral antidiabetic drugs), and for continuous subcutaneous insulin infusion (CSII) by external pump, where both basal and bolus requirements can be covered by Fiasp®. Fiasp® can be injected at the start of a meal or post-meal (within 20 minutes after starting a meal). [6]

Summary of evidence

Summary of efficacy data in proposed use:

The efficacy evaluation of Fiasp® (in the final formulation intended for the market) is based on three therapeutic confirmatory trials evaluating the efficacy and safety of Fiasp® in adult subjects (≥18 years old) with type 1 and type 2 diabetes mellitus. Patients were randomised following an 8-week run in to optimise basal insulin treatment. In addition, two trials provide supportive data evaluating Fiasp® for CSII by external pump. [6]

Onset 1 [1]

This 26-week (plus additional 26 weeks extension) multicenter, active-controlled, randomised, parallel-group trial compared double-blind mealtime Fiasp® with mealtime insulin aspart (NovoRapid®) in 1,143 adults with **type 1 diabetes**. The additional 26-week extension was an open-label study of post-meal Fiasp® and provided long-term safety data. Adults (≥18 years old) with type 1 diabetes (diagnosed clinically) were eligible for inclusion if treated with basal-bolus insulin for ≥12 months prior to screening and if treated with any regimen of insulin detemir or glargine for ≥4 months prior to screening, with an HbA_{1c} of 7.0–9.5% (53– 80 mmol/mol) and BMI of ≤35.0 kg/m^2. Exclusion criteria included any use of an antidiabetic drug other than insulin

within 3 months prior to screening, an anticipated change in concomitant medications known to interfere significantly with glucose metabolism, severe or unstable cardiovascular disease within 6 months prior to screening, recurrent severe hypoglycaemia (>1 event during the past 12 months), hypoglycaemic unawareness as judged by the investigator, or hospitalisation for diabetic ketoacidosis within 6 months prior to screening.

The primary end point was change from baseline in HbA_{1c} after 26 weeks. Noninferiority of Fiasp, both mealtime and post-meal dosing, to mealtime NovoRapid in terms of change from baseline in HbA_{1c} was confirmed (estimated treatment difference: mealtime Fiasp –0.15% [CI95% –0.23; –0.07]; post-meal Fiasp 0.04% [CI95% –0.04; 0.12], P=0.0001 for noninferiority).

The secondary outcome measure of estimated change from baseline in the 2-hour post-prandial glucose (PPG) increment (meal test) was –0.3 mmol/L with mealtime Fiasp and 0.4 mmol/L with NovoRapid (estimated treatment difference for mealtime Fiasp –0.67 mmol/L [CI95% –1.29; –0.04], P=0.0375). This treatment difference confirmed Superiority of mealtime Fiasp versus NovoRapid for 2-hour PPG increment. For post-meal Fiasp versus NovoRapid, 2-hour PPG increments (meal test) were not significantly different (estimated treatment difference 0.30 mmol/L [CI95% –0.34; 0.93].

Onset 2 [7]
As for onset 1, this was a 26-week multicentre, double-blind, active-controlled, parallel-group trial, although onset 2 randomised 691 adults with **type 2 diabetes** to either mealtime Fiasp or mealtime NovoRapid. Participants of the trial had been diagnosed with type 2 diabetes for 6 months or more; had received treatment with a basal insulin for at least 6 months prior to screening; received once-daily administration of NPH insulin, insulin detemir or insulin glargine in combination with unchanged oral diabetic drug regimen for ≥ 3 months; had an HbA_{1c} of 7.0–9.5% (53– 80 mmol/mol) and BMI of ≤40.0 kg/m^2. Exclusion criteria included any use of bolus insulin (except short term use ≤14 days); use of glucagon-like peptide 1 agonists and/or thiazolidinediones within 3 months of screening; anticipated change in medication likely to significantly interfere with glucose metabolism (e.g. corticosteroids, beta-blockers); severe or unstable cardiovascular disease within the 6 months prior to screening; impaired hepatic and/or renal function (creatinine clearance of 60mL/min); recurrent severe hypoglycaemia or hypoglycaemia unawareness as judged by the investigator, or hospitalisation for diabetic ketoacidosis during the 6 months prior to screening.

For the primary end point, HbA_{1c} change was –1.38% (Fiasp) and –1.36% (NovoRapid); mean HbA_{1c} was 6.6% for both groups. Fiasp demonstrated noninferiority versus NovoRapid in reducing HbA_{1c} (estimated treatment difference –0.02% [CI95% –0.15; 0.10]). Both treatments improved PPG control (secondary end point); the PPG increment was statistically significant in favour of Fiasp after 1 hour (estimated treatment difference−0.59 mmol/L [CI95% −1.09; −0.09], *P*=0.0198), but not after 2–4 hours.

Onset 3 [8]

In this open-label, randomised, 18-week trial, adults (n = 236) with inadequately controlled **type 2 diabetes** (mean HbA_{1c} 7.9% ±SD 0.7%) receiving basal insulin and oral antidiabetic drugs underwent 8-week optimisation of prior once-daily basal insulin followed by randomisation 1:1 to either a basal-bolus regimen with Fiasp (n = 116) or continuation of once-daily basal insulin (n = 120), both with metformin. Additional inclusion and exclusion criteria matched those in the design of the **onset 2** trial.

The aim of **Onset 3** was to confirm glycaemic control superiority of mealtime Fiasp in a basal-bolus regimen vs basal-only insulin. HbA_{1c} decreased from 7.9% to 6.8% (in the basal-bolus group) and from 7.9% to 7.7% (basal-only group); (estimated treatment difference −0.94% [CI95% −1.17; −0.72], P<0.0001). For the secondary end points, 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 the basal-bolus treatment (Estimated treatment difference −2.48 mmol/L [CI95% −2.92; −2.03], P < .0001).

Other efficacy data:

A randomised (1:1:1), double-blind, active-controlled, 3-way crossover CSII trial (trial 3930) was conducted in 43 subjects with type 1 diabetes mellitus on a pre-trial CSII regimen for ≥6 months with an insulin analogue for ≥3 months. The trials compared 3 different formulations of insulin aspart after 2 weeks of treatment with each, using CSII by external pump, with regard to 2-hour post-meal glucose response after a standardised meal and other efficacy, safety and pump related endpoints. Subjects were randomised to receive the trial products (Fiasp, NovoRapid and FIA(R); an earlier formulation of Fiasp not pursued for further development) in one of six treatment sequences in this crossover trial.

In trial 3930, a statistically significantly greater glucose-lowering effect was demonstrated with Fiasp compared to NovoRapid in terms of mean change in the plasma glucose concentration during the first 2 hours of a standardised meal test (estimated treatment difference: -0.99 mmol/L [CI95% -1.95; -0.03]). The mean change over the first hour after the meal pointed in the same direction. Fiasp was comparable to NovoRapid across most other endpoints related to overall glucose control. The finding of a lower post-meal glucose increment with Fiasp as compared to NovoRapid was supported by mean prandial interstitial glucose increments during 14 days of continuous glucose monitoring that were statistically significantly lower for Fiasp at 1 hour and 2 hours after all meals.

Summary of safety data:

The safety information for Fiasp was based on two 26-weeks completed basal-bolus trials (including a 26-week extension study) in subjects with type 1 and 2 diabetes (**onset 1 and onset 2**). Three other completed therapeutic confirmatory and exploratory trials **onset 3** (18 weeks in type 2 diabetics), 3931 (6 weeks in type 1) and 3930 (type 1) were used to support the safety evaluations from the 2 basal-bolus trials. In addition, the use of Fiasp in CSII with pumps was based in another two trials (3930 and 3931). [6]

Hypoglycaemia

In total, approximately 98% of the subjects in **onset 1** and approximately 94% of the subject in **onset 2** experienced any event of hypoglycaemia. Severe or blood glucose confirmed hypoglycaemic episodes were reported in 8% of the subjects with type 1 diabetes (**onset 1**) during the trial compared to 3.5% in the patients with type 2 diabetes (**onset 2**). Thus, a higher rate and frequency of both hypoglycaemic events in total as well as severe and blood glucose confirmed hypoglycaemic events were, as expected, more common in patients with type 1 diabetes compared to patients with type 2 diabetes. There was no significant difference in the frequencies of hypoglycaemic episodes between the two formulations in either of the trials. There were no differences between the two formulations regarding hypoglycaemia over time of day (daytime and nocturnal hypoglycaemia) or accumulation rate of hypoglycaemia over the trial duration.

The mealtime Fiasp had a statistically significant higher rate of hypoglycaemic episodes (severe or BG confirmed) the first hour after meal compared to NovoRapid in patients with type 1 diabetes. Two hours after meal a difference was still present but this was not significant. The group randomised to post-meal Fiasp had rates of hypoglycaemic events similar to the subjects using NovoRapid. For patient with type 2 diabetes there was a statistically significant difference with higher rates of corresponding definitions of hypoglycaemic episodes two hours after meal (a difference was also seen the first hour after meals but this was not statistically significant). [6]

Body weight

In **onset 1** in subjects with type 1 diabetes, mean body weight increased slightly from baseline to week 26 in all 3 treatment groups (0.67 kg for Fiasp (meal), 0.70 kg for Fiasp (post-meal) and 0.55 kg NovoRapid, respectively). There was no statistically significant treatment difference after 26 weeks of treatment. [1]

In **onset 2**, in subjects with type 2 diabetes, mean body weight increased from baseline in both treatment groups to a similar extent, with no statistically significant difference between treatments

after 26 weeks (2.67kg for Fiasp and 2.68 kg for NovoRapid). [7]

In **onset 3**, in subjects with type 2 diabetes, a statistically significantly greater mean body weight increase was observed in the Fiasp + basal treatment group as compared to the basal group after 18 weeks of treatment (1.83 kg for Fiasp and 0.17 kg for basal insulin). The mean weight gain in the Fiasp + basal group was still below 2 kg and of the magnitude expected when adding bolus insulin to an insulin regimen. [8]

Other adverse events

Excluding hypoglycaemia, the sponsor reported no serious adverse events occurring in ≥1% of subjects. In total 5 deaths were reported after randomisation in the completed clinical trials. However, the risk of deaths seemed not to reflect a difference between Fiasp and NovoRapid nor an apparent association between insulin aspart and mortality risk.

A list of the adverse reactions for Fiasp from the Summary of Products characteristics are included below: [3]

MedDRA System Organ Class	Very common	Common	Uncommon
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders	Hypoglycaemia		
Skin and subcutaneous tissue disorders		Allergic skin manifestations	Lipodystrophy
General disorders and administration site conditions		Injection/infusion site reactions	

The SPC warns that the safety profile in patients ≥ 75 years or patients with severe renal/hepatic impairment is limited and Fiasp should be used with caution in these groups of patients.

Strengths and limitations of the evidence:

Strengths:

- The design of the onset studies was robust with a large subject enrolment and data for up to 1 year.
- **Onset 1** demonstrated noninferiority of Fiasp, for both mealtime and post-meal dosing, compared to mealtime NovoRapid in terms of change from baseline in HbA_{1c} in type 1 diabetic patients (and superiority for mealtime Fiasp versus mealtime NovoRapid).
- **Onset 2** supported the results of **onset 1** demonstrating noninferiority of mealtime Fiasp with mealtime NovoRapid in terms of change from baseline in HbA_{1c} in type 2 diabetic patients.
- Both **onset 1** and **onset 2** demonstrated superior post prandial glucose control at 1 hour for mealtime Fiasp compared to mealtime NovoRapid.
- Superior post prandial control offered by Fiasp use may benefit pregnant patients trying to achieve tighter post prandial glycaemic control in line with the NICE guideline for pregnancy. [9]
- Apart from differences in the timing of the hypoglycaemic episodes, no significant differences of clinical importance in the pattern, proportions and rates of adverse events were identified between Fiasp and NovoRapid in either type 1 or type 2 diabetes mellitus.

Limitations:

- It may be considered that the documented differences in efficacy or safety (i.e. Changes in glycaemic control and/or the timing of hypoglycaemias) between Fiasp and NovoRapid are not of sufficient clinical relevance to consider Fiasp a different medicinal product.
- There are no comparative studies of post-meal NovoRapid versus post-meal Fiasp.
- In the **onset 1** and **onset 2** trials, the rates of hypoglycaemic events at 1 hour and 2 hours post-meal were greater in the Fiasp patient group than the NovoRapid patient group.
- The improvement in PPG control 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 HbA_{1c}. Further, the effect of improved PPG control decreased over time.
- The **Onset 3** study supported the use of basal-bolus insulin in patients inadequately controlled on basal insulin, although the study did not provide any additional evidence to support the use of Fiasp over other bolus insulins.
- There was an apparent increase in the frequency of injection site reactions in the Fiasp group compared to the NovoRapid especially in type 1 diabetic patients.

Summary of evidence on cost effectiveness:

No cost effectiveness evidence is available for Fiasp, however the Scottish Medicines Consortium has accepted Fiasp for use within NHS Scotland as it is available at an equivalent cost to other insulin aspart formulations. [10]

Prescribing and risk management issues:

The Summary of Product Characteristics for Fiasp contains a caution regarding the avoidance of accidential mix-ups / medication errors as data from the onset trials suggested that this was the most common cause of serious adverse events.

Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between this medicinal product and other insulin medicinal products. [3]

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Insulin aspart (Fiasp®) FlexTouch 100unit/ml pre-filled pen	Dosage according to requirements. Assuming total daily dose of 20-40 units	£30.60	£149 - £298
Insulin aspart (Fiasp®) Penfill 100unit/ml cartridges	Dosage according to requirements. Assuming total daily dose of 20-40 units	£28.31	£138 - £276
Insulin aspart (NovoRapid®) FlexPen 100unit/ml pre-filled pen	Dosage according to requirements. Assuming total daily dose of 20-40 units	£30.60	£149 - £298
Insulin aspart (NovoRapid®) FlexTouch 100unit/ml pre-filled pen	Dosage according to requirements. Assuming total daily dose of 20-40 units	£32.13	£157 - £313
Insulin aspart (NovoRapid®) Penfill 100unit/ml cartridges	Dosage according to requirements. Assuming total daily dose of 20-40 units	£28.31	£138 - £276
Insulin glulisine (Apidra®) 100unit/ml cartridges	Dosage according to requirements. Assuming total daily dose of 20-40 units	£28.30	£138 - £276
Insulin glulisine (Apidra®) SoloStar 100unit/ml pre-filled pen	Dosage according to requirements. Assuming total daily dose of 20-40 units	£28.30	£138 - £276
Insulin lispro (Humalog®) 100unit/ml cartridges	Dosage according to requirements. Assuming total daily dose of 20-40 units	£28.31	£138 - £276
Insulin lispro (Humalog®) KwikPen 100unit/ml pre-filled pen	Dosage according to requirements. Assuming total daily dose of 20-40 units	£29.46	£144 - £287
Costs based on MIMS list prices July 2017. This table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

It is assumed that other costs including needles, test strips and concomitant medicines would be equal for each of the bolus-insulins.

Productivity, service delivery, implementation:

It is anticipated that Fiasp may be initiated by prescribers in both primary care and specialist settings.

Anticipated patient numbers and net budget impact:

According to ePACT data in the year to April 2017, across the Lancashire health economy approximately 50,000 items of NovoRapid were prescribed at a total cost of approximately £2,000,000. As Fiasp is the same price as NovoRapid, no additional cost is anticipated.

Innovation, need, equity:

Insulin aspart (Fiasp) is a new formulation with a faster onset of action than another formulation of insulin aspart and is available at an equivalent cost. However, there is some conjecture as to whether Fiasp is a separate medicinal product to NovoRapid.

References

[1] Russell-Jones D et al, "Fast-Acting Insulin Aspart Improves Glycaemic Control in Basal-Bolus Treatment for Type 1 Diabetes: Results of a 26-Week Multicenter, Active-Controlled, Treat-to-Target, Randomised, Parallel-Group Trial (onset 1)," *Diabetes care,* vol. 40, pp. 943-950, 2017.

[2] National Institute for Health and Care Excellence, "Clinical Guideline [NG17] Type 1 diabetes in adults: diagnosis and management," August 2015. [Online]. Available: https://www.nice.org.uk/guidance/ng17. [Accessed 10 July 2017].

[3] Electronic Medicines Compendium, "Summary of Product Characteristics for Fiasp," Novo Nordisk Limited, 27 February 2017. [Online]. Available: https://www.medicines.org.uk/emc/medicine/33022. [Accessed 10 July 2017].

[4] National Institute of Health and Care Excellence, "Clinical Guideline [NG28] Type 2 diabetes in adults: management," 12 2015. [Online]. Available: https://www.nice.org.uk/guidance/ng28. [Accessed 10 July 2017].

[5] World Health Organisation (WHO), "Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus," Report number: WHO/NCD/NCS/99.2, Geneva, 1999.

[6] European Medicines Agency, "European Public Assessment Report- Fiasp," 10 November 2016. [Online]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004046/WC500220940.pdf. [Accessed 10 July 2017].

[7] Bowering K et al, "Faster Aspart Versus Insulin Aspart as Part of a Basal-Bolus Regimen in Inadequately Controlled Type 2 Diabetes: The onset 2 trial," *Diabetes Care,* vol. 40, no. 7, pp. 951-957, 2017.

[8] Rodbard H et al, "Adding fast-acting insulin aspart to basal insulin significantly improved glycaemic control in patients with type 2 diabetes: A randomised, 18-week, open-label, phase 3 trial (onset 3)," *Diabetes, Obesity and Metabolism,* pp. 1-8, 2017.

[9] National Institute for Health and Care Excellence, "Diabetes in pregnancy: management from preconception to the postnatal period," February 2015. [Online]. Available: https://www.nice.org.uk/guidance/ng3. [Accessed 18 July 2017].

[10] Scottish Medicines Consortium, "Insulin aspart (Fiasp) 100units/mL solution for injection in vial; solution for injection in cartridge (Penfill); solution for injection in pre-filled pen (FlexTouch)," 10 March 2017. [Online]. Available: https://www.scottishmedicines.org.uk/files/advice/insulin_aspart_Fiasp_Abbreviated_FINAL_March_2017_for_website.pdf. [Accessed 19 July 2017].

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