

**5.08 INSULIN ASPART,  
Injections, 100 units per mL, 1 x 10 mL vial  
Injections, 100 units per mL, 5 x 3 mL cartridges  
Injections, 100 units per mL, 5 x 3 mL injection devices  
Fiasp<sup>®</sup>, Novo Nordisk Pharmaceuticals Pty Ltd**

**1 Purpose of Application**

- 1.1 The submission requested an unrestricted listing for insulin aspart (Fiasp<sup>®</sup>) for treatment of type 1 and type 2 diabetes mellitus (T1DM and T2DM).
- 1.2 An existing formulation of insulin aspart (NovoRapid<sup>®</sup>) is already listed on the PBS. The new formulation, Fiasp, has a faster onset of action resulting from the addition of the excipient niacinamide.
- 1.3 Table 1 summarises key components of the clinical issues addressed by the submission.

**Table 1: Key components of the clinical issues addressed by the submission**

| <b>Component</b> | <b>Description</b>   |
|------------------|--|
| Population       | Patients with Type 1 and Type 2 diabetes mellitus requiring bolus insulin.   |
| Intervention     | Insulin aspart (Fiasp) delivered either as bolus subcutaneous injections or via external continuous subcutaneous insulin infusion (CSII).                      |
| Comparator       | Insulin aspart (NovoRapid)   |
| Outcomes         | Glycaemic control measured by mean decrease in HbA1c, post prandial glucose, rates of hypoglycaemia.   |
| Clinical claim   | The submission claimed insulin aspart (Fiasp <sup>®</sup> ) to be no worse than insulin aspart (NovoRapid) at improving HbA1c and no worse in terms of safety. |

Source: compiled during the evaluation based on information contained in Table 1.1.1, p17 of the submission.

**2 Requested listing**

- 2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough

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| Name, restriction, manner of administration, form                       | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Dispensed price for maximum quantity (DPMQ) | Proprietary name and manufacturer |
|---|--------------------------|--------------------------|----------------|---|-----------------------------------|
| Fast-acting insulin aspart, 100units/mL injection, 1x10mL vial          | 5                        | 5                        | 2              | \$143.39*                                   | Fiasp Vial, Novo Nordisk          |
| Fast-acting insulin aspart 100units/mL injection, 5x3mL pre filled pens | 5                        | 5                        | 1              | \$240.84*                                   | Fiasp FlexTouch, Novo Nordisk     |
| Fast-acting insulin aspart 100units/mL injection, 5x3mL cartridges      | 5                        | 5                        | 1              | \$240.84*                                   | Fiasp Penfill, Novo Nordisk       |

\*updated during the evaluation based on sponsor prices stated in PB11 using latest dispensing and administration, handling and infrastructure (AHI) fees from 1 July 2018.

Source: Adapted using Table 1.4.1, p32 of the submission and PB11 form accompanying the submission.

- 2.2 An unrestricted PBS listing was requested for Fiasp, which is consistent with the listing of other fast acting insulin preparations on the PBS.
- 2.3 The submission requested that, as per Section 5.7 of the Strategic Agreement between the Commonwealth and Medicines Australia, the DPMQ of Fiasp be equivalent to the price of NovoRapid prior to the application of the 14.5% Statutory Price Reduction that was applied on 1 June 2018. The ESC noted that this is a matter for the Minister (or delegate).
- 2.4 The PSCR highlighted that the submission assumed that Section 99ACB of the *National Health Act 1953* did not apply to Fiasp and NovoRapid, that is, that Fiasp was not a new brand of the existing pharmaceutical item insulin aspart given their different pharmacokinetic and pharmacodynamics profiles.
- 2.5 The potential use of Fiasp on the PBS may be broader than its TGA approved indication, which is for treatment of diabetes mellitus in adults. The lack of data for safety and efficacy in children was a concern for the TGA, particularly as more children are affected by T1DM. The TGA evaluator considered the use of a fast acting insulin with meals has many advantages in children (particularly toddlers), where food refusal can be problematic. The TGA considered off label use in this population was therefore likely. Given the unrestricted nature of the requested listing, use in children would also be likely on PBS. Additionally NovoRapid is approved for use in both children and adults. The PSCR stated that clinical data on use of Fiasp in paediatrics with T1DM has become available and that should Fiasp become listed on the PBS, the sponsor would consider seeking TGA registration in paediatric patients.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

### **3 Background**

#### ***Registration status***

- 3.1 Fiasp (in vial, Penfill and Flextouch preparations) was approved by the TGA (28 June 2017) for the following indication: “Treatment of diabetes mellitus in adults”.

#### ***Previous PBAC consideration***

- 3.2 This was the first PBAC submission for Fiasp. The existing formulation of insulin aspart, NovoRapid, was considered by the PBAC in March 2000 and was first listed on the PBS in 2002.

### **4 Population and disease**

- 4.1 Diabetes (type 1 and type 2) is a chronic metabolic disorder characterised by elevated levels of blood glucose. Long-term complications of the disease, which are a consequence of continuously prolonged hyperglycaemia, include retinopathy, nephropathy, neuropathy and cardiovascular disease (Campbell and Martin 2009). These complications have a considerable impact on health, a negative impact on health-related quality of life (HRQoL) (Rubin and Peyrot 1999, UK Prospective Diabetes Study Group 1999), and represent a significant proportion of the economic burden of diabetes mellitus (Baker IDI Heart and Diabetes Institute in partnership with Diabetes Australia and Juvenile Diabetes Research Foundation (JDRF) 2012, Schofield et al. 2017).
- 4.2 Insulin aspart (Fiasp) will provide another treatment option for patients with T1DM and T2DM requiring a combination of a basal and a prandial insulin to maintain appropriate glycaemic control.

### **5 Comparator**

- 5.1 The submission nominated insulin aspart (NovoRapid) as the main comparator. While three fast acting insulins are listed on the PBS (insulin aspart (NovoRapid®), insulin lispro (Humalog®) and insulin glulisine (Apidra®)), PBS utilisation data indicated insulin aspart (NovoRapid®) to have approximately 80% of the current market share.
- 5.2 The submission considered that despite differing formulations, NovoRapid was the appropriate main comparator as it contains the same drug as Fiasp.
- 5.3 The nomination of the main comparator was reasonable; however, given all fast acting insulins were listed on a cost minimisation basis to each other, all PBS listed fast acting insulins could therefore be replaced by Fiasp in practice. Based on the PBS Therapeutic Relativity Sheets:
- insulin lispro (Humalog) was accepted for listing on the basis of advantage (taken directly before a meal) over short acting insulin;

- insulin aspart (NovoRapid) was accepted on a cost minimisation basis compared with insulin lispro (unit for unit); and
  - insulin glulisine (Apidra) was recommended for listing on a cost minimisation basis compared to insulin lispro with the equi-effective doses being 1 unit of insulin glulisine = 1 unit of insulin lispro.
- 5.4 Current PBS listings indicate NovoRapid and Humalog to have identical pricing on a unit to unit basis, whereas the DPMQs of insulin glulisine (Apidra) are approximately 5% higher for both its cartridge and vial formulations.
- 5.5 The ESC considered the main comparator to be reasonable due to similarity in formulation. The ESC noted that other fast acting insulins listed on the PBS may also be relevant comparators.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from a health care professional (1) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments described the positive impact on target blood glucose levels obtained through an insulin product that can be administered with, rather than prior to, a meal.
- 6.3 The PBAC noted the advice received from JDRF Australia welcoming any product that allows for faster action of insulin in the T1DM community.

### ***Clinical trials***

- 6.4 The submission was based on four head-to-head randomised trials comparing Fiasp to NovoRapid. The trial evidence included:
- One RCT in patients with T2DM (bolus/basal regimen): onset 2 (results reported at 26 weeks).
  - Three RCTs in patients with T1DM:
    - One RCT using bolus/basal regimen: onset 1 (results reported at 26 and 52 weeks); and
    - Two RCTs of using continuous subcutaneous insulin infusion (CSII) systems: onset 4 and onset 5 (results reported at 6 and 16 weeks, respectively). The onset 4 trial was a short trial of 6 weeks treatment duration, with the primary objective of evaluating the compatibility of Fiasp and NovoRapid® with CSII, it was therefore considered to be supportive evidence to the onset 5 trial.

6.5 The ESC noted only a single study was provided to support the claim of non-inferiority for T2DM patients.

6.6 With the exception of onset 4, all included trials were non-inferiority trials reporting the primary outcome: change from baseline in glycosylated haemoglobin (HbA1c), with the pre-specified non-inferiority margin of 0.4%. The submission’s non-inferiority claim was also based on this outcome and margin. Both the nominated outcome and non-inferiority margin had previously been accepted by the PBAC. The ESC noted that this outcome was reasonable.

6.7 Details of the trials presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

| Trial ID           | Protocol title/ Publication title  | Publication citation   |
|--------------------|--|--|
| onset 1(26 weeks)  | Efficacy and Safety of FIAsp Compared to Insulin Aspart Both in Combination with Insulin Detemir in Adults with Type 1 Diabetes.<br><br>Russell-Jones D, Bode BW, De Block C et al. Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: Results of a 26-week multicentre, active-controlled, treat-to-target, randomised, parallel-group trial (onset 1).       | September 2015<br><br>Diabetes Care 2017; 40(7):943-950                                |
| onset 1 (52 weeks) | Efficacy and Safety of FIAsp Compared to Insulin Aspart Both in Combination with Insulin Detemir in Adults with Type 1 Diabetes. This report covers the entire 52-week treatment period.<br><br>Mathieu C, Bode BW, Franek E et al. Efficacy and safety of fast-acting insulin aspart in comparison with insulin aspart in type 1 diabetes (onset 1): A 52-week, randomized, treat-to-target, phase III trial. | January 2016<br><br>Diabetes Obes Metab. 2018; 20: 1148-1155.                          |
| onset 2            | Efficacy and Safety of FIAsp Compared to Insulin Aspart Both in Combination with Insulin Glargine and Metformin in Adults with Type 2 Diabetes.<br><br>Bowering K, Case C, Harvey J et al. Faster aspart versus insulin aspart as part of a basal-bolus regimen in inadequately controlled type 2 diabetes: The onset 2 trial.   | September 2015<br><br>Diabetes Care 2017; 40:951-957.                                  |
| onset 4            | A 6-Week Randomised, Double-Blind, Parallel-Group Trial Evaluating Compatibility and Safety of FIAsp and Insulin Aspart with an External Continuous Insulin Infusion System in Adult Subjects with Type 1 Diabetes.<br><br>Zijlstra E, Demissie M, Graungaard T et al. Investigation of pump compatibility of fast-acting insulin aspart in subjects with type 1 diabetes.                                     | September 2015<br><br>Journal of Diabetes Science and Technology 2018; 12(1): 145-151. |
| onset 5            | Efficacy and Safety of Continuous Subcutaneous Insulin Infusion of Faster-acting Insulin Aspart compared to NovoRapid® in Adults with Type 1 Diabetes.   | February 2018  |

Note: only main trial citations have been included in this table.

<sup>a</sup> This trial appears to only be identified in the submission from a literature search conducted in PubMed on 30<sup>th</sup> May 2018 to identify any additional studies pertaining to the safety profile on Fiasp.

Source: Table 2.2.2, pp.39-41 of the submission.

6.8 The key features of the direct randomised trials are summarised in Table 3.

**Table 3: Key features of the included evidence**

| Trial   | N    | Design/ duration   | Risk of bias                                      | Patient population   | Main Outcomes   | Use in modelled evaluation |
|---|------|--|---|--|---|----------------------------|
| <b>Fast aspart (Fiasp) versus insulin aspart (NovoRapid®)</b> |      |  |   |  |   |                            |
| onset 1 (26 weeks data)                                       | 1143 | R, MC, P3, AC, TTT, DB (meal time dose arms Fiasp and NovoRapid®) and open label post meal Fiasp dose arm, non-inferiority approach, 8W run-in*, W26 to W52 only compared the 2 mealtime insulin arms (investigator and participant remain blinded to assignment, but the sponsor became unblinded). | Low (for mealtime arms)<br>High for post meal arm | Adults with T1DM, use in combination with daily or BD insulin detemir (NovoLog®)             | Δ HbA1c W26<br>Δ PPG<br>Δ body weight<br>Hypoglycaemia events   | NA                         |
| onset 1 (52 weeks data)                                       | 1143 |  | Unclear   |  | Δ HbA1c W52<br>Δ PPG<br>Δ body weight<br>Hypoglycaemia events   | NA                         |
| onset 2   | 689  | R, MC, DB, P3, AC, TTT, 8W run in*, 26W treatment, non-inferiority approach  | Low   | Adults with T2DM, in combination with insulin glargine and metformin, baseline HbA1c 7-9.5%. | Δ HbA1c W26<br>Δ PPG<br>Δ body weight<br>Hypoglycaemia events   | NA                         |
| onset 4 (CSII)  | 37   | R, 2 centre, P3a, DB, 2W run in#, 6W treatment, administration via CSII.   | Low   | Adults with T1DM, no additional anti-diabetes treatments allowed.                            | Safety & feasibility of CSII W6<br>Δ HbA1c W6<br>Δ PPG<br>Hypoglycaemia events<br>Infusion set occlusion events | NA                         |
| onset 5 (CSII)  | 472  | R, MC, DB, P3b, AC, TTT, 4W run in^, 26W treatment, administration via CSII non-inferiority approach   | Low   | Adults with T1DM   | Δ HbA1c W26<br>Δ PPG<br>Δ body weight<br>Hypoglycaemia events<br>Infusion set changes                           | NA                         |

Abbreviations: DB=double blind; MC=multi-centre; OL=open label; AC=active controlled, TTT=treat to target, R=randomised, CSII=continuous subcutaneous insulin infusion, W=weeks, BD=twice daily, HbA1c=glycosylated haemoglobin, P=phase.

\* to optimise basal insulin

# during the 2 week run in period, all subjects were switched from their previous rapid-acting analog treatment to insulin aspart. Subjects' knowledge on using an insulin pump, handling of transfusion sets, and keeping a travel diary was reinforced.

^ The 4-week run-in period was primarily for reinforcement of subject training in trial procedures, diabetes education and collecting baseline assessments

Source: compiled during evaluation based on information presented on pp42-44 of the submission.

6.9 Attrition and overall risk of bias was low in each of the key trials except for onset 1. In onset 1, treatment assignment to the post meal Fiasp was unblinded to patients and investigators, and beyond Week 26, although the investigators and participants remained blinded to treatment assignment in the other two meal time dose arms, concealment was broken to the sponsor. While the full implication of unblinded treatment was unclear, as the main outcome was change in HbA1c from baseline, which was an objective measurement, it was unlikely to be impacted significantly.

- 6.10 Flow of patients through the randomised double-blind treatment period: each trial included a run-in period prior to randomisation. The numbers of patients lost to follow up or discontinued were similar between the treatment arms in the included trials. The most common reason for discontinuation was decision by subject.
- 6.11 Key inclusion and exclusion criteria in the included trials: the trials generally enrolled similar patient populations, consisting of adult diabetic patients. The main difference was that the onset 2 trial enrolled T2DM patients whilst the other three trials enrolled T1DM patients. All trials required patients to have inadequate glycaemic control at trial entry, demonstrated by a HbA1c level of between 7.0% and 9.5% in onset 1 and onset 2, between 7.0% and 9.0% in onset 5, and a level of less or equal to 9.0% in onset 4. In clinical practice, inadequate glycaemic control is indicated by a HbA1c level > 7.0%.
- 6.12 Baseline patient characteristics: randomisation appeared successful within most trials. Where differences were detected, the noted differences were small and were unlikely to impact on the results. Between the trials, patient characteristics at baseline were broadly similar in patients with T1DM (onset 1, onset 4 and onset 5). Patients with T2DM (onset 2) were on average older (59.5 years in onset 2 versus 34.7-46.1 years), heavier (88-89 kg vs 76 and 84 kg) and had higher baseline BMI ( $\approx 31$  kg/m<sup>2</sup> vs 25-27 kg/m<sup>2</sup>) than T1DM patients in other included trials. Consistent with the natural history of the disease, T2DM patients in the onset 2 trial also had the shortest duration of diabetes (12.3-13.2 years) versus T1DM patients (19.3-25.9 years).
- 6.13 Broadly, the included trials employed similar dosing regimens with similar target blood glucose levels for basal and bolus insulin doses. The dosing of Fiasp, NovoRapid and concomitant medications were also consistent with the PIs, and reflected recommended Australian practice. The majority of the trials had compared meal time Fiasp to meal time NovoRapid, with the exception of the onset 1 trial, which also included an open label treatment arm administering Fiasp at 20 minutes after the start of the meal.
- 6.14 The ESC noted the trial evidence provided with the submission and agreed that the data were broadly applicable to the Australian setting.

### ***Comparative effectiveness***

- 6.15 Table 4 summarises the main outcomes from the included trials.

Table 4: Summary of main outcomes in the trials

| Trial ID            | Comparison                      | Diff in $\Delta$ HbA1c<br>(%, 95% CI) <sup>a</sup> | Diff in % patient attaining<br>RD (95% CI) <sup>a</sup> |                        | $\Delta$ PPG increment (mmol/L)<br>(%, 95% CI) <sup>a</sup> |                                       | $\Delta$ body<br>weight (kg)<br>(%, 95% CI) <sup>a</sup> | Diff in<br>hypoglycaemic<br>events <sup>d</sup><br>rate ratio<br>(95% CI) <sup>c</sup> |
|---------------------|---------------------------------|--|---|------------------------|---|---------------------------------------|--|--|
|                     |                                 |  | HbA1c <7.0%   | HbA1c $\leq$ 6.5%      | 1h post meal  | 2h post meal                          |  |  |
| onset 1<br>(26 wks) | Fiasp meal vs<br>NovoRapid®     | <b>-0.15</b><br><b>(-0.23; -0.07)</b>              | 0.05<br>(-0.01, 0.12)                                   | 0.02<br>(-0.03, 0.07)  | <b>-1.18</b><br><b>(-1.65, -0.71)</b>                       | <b>-0.67</b><br><b>(-1.29, -0.04)</b> | 0.12<br>(-0.30, 0.55)                                    | 1.01<br>(0.88, 1.15)   |
|                     | Postmeal Fiasp vs<br>NovoRapid® | 0.04<br>(-0.04; 0.12)                              | -0.05<br>(-0.11, 0.01)                                  | -0.04<br>(-0.09, 0.00) | <b>0.93</b><br><b>(0.46, 1.40)</b>                          | 0.30<br>(-0.34, 0.93) <sup>h</sup>    | 0.16<br>(-0.27, 0.58)                                    | 0.92<br>(0.81, 1.06)   |
| onset 1<br>(52 wks) | Meal Fiasp vs<br>NovoRapid      | <b>-0.10</b><br><b>(-0.19; -0.00)</b>              | -0.01<br>(-0.07, 0.05)                                  | 0.00<br>(-0.04, 0.04)  | <b>-0.91</b><br><b>(-1.40, -0.43)</b>                       | -0.42<br>(-1.11, 0.27)                | 0.13<br>(-0.38, 0.65)                                    | 1.01<br>(0.88, 1.15)   |
| onset 2             | Meal Fiasp vs<br>NovoRapid      | -0.02<br>(-0.15; 0.10)                             | -0.01<br>(-0.08, 0.05)                                  | -0.02<br>(-0.09, 0.06) | <b>-0.59</b><br><b>(-1.09, -0.09)</b>                       | -0.36<br>(-0.81, 0.08)                | 0.00<br>(-0.60, 0.61)                                    | 1.09<br>(0.88, 1.36)   |
| onset 4<br>(6wks)   | CSII: Fiasp vs<br>NovoRapid®    | <b>-0.14</b><br><b>(-0.40, 0.11)</b>               | 0.19<br>(-0.09, 0.48)                                   | 0.16<br>(-0.07, 0.39)  | -   | -0.77<br>(-2.06, 0.51)                | -  | -  |
| onset 5             | CSII: Fiasp vs<br>NovoRapid®    | 0.09<br>(0.01; 0.17)                               | -0.03<br>(-0.10, 0.05)                                  | -                      | <b>-0.91</b><br><b>(-1.43, -0.39)</b>                       | <b>-0.90</b><br><b>(-1.58, -0.22)</b> | -0.43<br>(-0.81, -0.06)                                  | 1.00<br>(0.85, 1.16)   |

Bolded typography indicates statistically significant results.

Abbreviations: PPG, postprandial glucose, BG, blood glucose

<sup>a</sup> Intervention versus NovoRapid®, <sup>b</sup> All hypoglycaemic events, <sup>c</sup> Rate ratio of events/100 patient years of exposure was calculated on FAS <sup>d</sup> severe or BG confirmed

Source: compiled during the evaluation, using Tables 2.5.1, 2.6.1-2.6.2 and ES.3 of the submission.

### HbA1c outcomes in the trials

6.16 The ESC agreed that based on HbA1c outcomes from the included trials, the submission's claim of non-inferiority between Fiasp and NovoRapid® appears reasonable. The following results were noted:

- Both Fiasp (administered 0-2min before meal or 20min after the start of a meal) and NovoRapid (administered 0-2min before meal) were associated with significant reductions in HbA1c from baseline.
- In patients with T1DM, the reductions in HbA1c were significantly larger for meal time Fiasp versus NovoRapid in the onset 1 trial, at both 26 and 52 weeks, difference (95%CI): -0.15 (-0.23, -0.07) and -0.10 (-0.19, -0.00), supporting the conclusion of non-inferiority. As superiority was not part of the testing procedure, superiority of Fiasp cannot be concluded from these results. It was noted the direction of effect was opposite for the comparison of post meal Fiasp versus NovoRapid (difference (95%CI): 0.04 (-0.04, 0.12)) and in onset 5 after 16 weeks of CSII administration (difference (95%CI): 0.09 (0.01, 0.17)). However despite this, as the results did not reach statistical significance and the upper 95%CI of estimated mean differences in HbA1c did not exceed the predefined non-inferiority margin of 0.4%, a conclusion of non-inferiority appeared to be supported.
- For patients with T2DM, no significant difference was observed between meal time Fiasp and NovoRapid with respect to HbA1c reduction in the onset 2 trial (difference (95%CI): -0.02 (-0.15, 0.10)), satisfying non-inferiority.

- Supportive evidence also indicated there to be no significant difference between Fiasp and NovoRapid® in terms of HbA1c responders (defined as achieving either HbA1c <7% or ≤6.5%) in any of the included trials at any assessment time point.

### **Other secondary outcomes of glucose control**

6.17 Secondary outcomes in glucose control generally supported the conclusion of non-inferiority between Fiasp and NovoRapid, some notable results were:

- In terms of difference in change from baseline in post prandial glucose (PPG) increment (meal test), owing to its faster onset of action, when administered at meal time, the results generally favoured Fiasp and were statistically significant for measurements taken 1 hour post meal. However, by 2 hours post meal, the differences were no longer significant except for in onset 1 at 26 weeks and in onset 5 at 16 weeks. Importantly, it was noted that post meal Fiasp performed significantly worse than NovoRapid in the 1 hour post meal PPG test (difference (95%CI): 0.93 (0.46, 1.40)), however the difference was no longer significant at the 2 hour mark (difference (95%CI): 0.30 (-0.34, 0.93)). The Pre-Sub Committee Response (PSCR) reiterated the sponsor's view that the reduction in post prandial glucose (PPG) at 1 and 2 hours post meal was clinically significant; however, the ESC questioned whether the dosing flexibility is clinically meaningful for patients. Further, the ESC considered that there was a lack of data in patients with Type 2 Diabetes Mellitus (T2DM), particularly in relation to post prandial hypoglycaemia.
- Overall, no meaningful differences were observed in the number of severe or blood glucose (BG) confirmed hypoglycaemic events between Fiasp and NovoRapid. Numerically, fewer events were observed for T1DM patients in onset 1 for patients treated with Fiasp (including significantly fewer patients with events) whereas more events were observed for Fiasp treated patients in the T2DM trial (onset 2) and the T1DM CSII trials (onset 4 and onset 5). The ESC noted that for the single trial presented for T2DM patients, there were numerically more hypoglycaemic events observed in the Fiasp trial arm.
- The mean body weight of trial participants generally increased over the trial duration (0.36-2.68kg), but were generally similar between those treated with Fiasp and NovoRapid. In onset 5, although the weight increase from baseline after 16 weeks was statistically significantly larger for NovoRapid versus Fiasp, the submission did not consider this small difference (-0.43kg (95%CI: -0.81, -0.06)) to be clinically relevant.

### **Occlusion events in infusion sets**

6.18 Occlusion events in the CSII trials (onset 4 and onset 5): no microscopically confirmed occlusive events were observed in the 6 week treatment duration of trial onset 4. There were however, 7 possible but unconfirmed set occlusions (reported by 5 (20%) of the patients) for patients treated with Fiasp and none for those treated with

NovoRapid. In the onset 5 trial, significantly more patients reported non-routine changes of infusion set with Fiasp (CSII) compared with NovoRapid (CSII) (71.2% versus 57.2%); however, despite this, a similar rate of non-routine infusion set changes per 100 person years was observed with Fiasp (CSII) compared to NovoRapid (CSII) (697 versus 668). The most frequently reported reason contributing to this was problems related to the infusion set. Changes in the category 'infusion site reaction' were numerically higher for Fiasp. A similar rate of changes in the category 'any problems related to the infusion set' was observed, despite a higher proportion of subjects with Fiasp than with NovoRapid. It is uncertain whether a higher proportion of patients with infusion set issues with Fiasp is likely to have resource implications in clinical practice. The ESC noted that the most common use of Fiasp may be in patients with insulin pumps and noted the higher number of occlusion events observed in the Fiasp trial arms which may translate to increased infusion set changes and associated costs in the real world setting.

### ***Comparative harms***

- 6.19 The incidence of any AE, serious AE, and discontinuations due to AE, were similar between the treatment groups. The most frequently reported AEs for both Fiasp and NovoRapid were nasopharyngitis (onset 1, 2 and 4), and upper respiratory tract infection (onset 1, 2 and 5). Adverse events of interest presented by the submission were medication errors concerning trial products (onset 1, onset 2 and onset 5) and cardiovascular events (onset 1 and onset 2). The incidence of these events were also similar across the treatment groups. It was noted by the submission (p119) that the only reported AE that significantly differed in frequency was upper abdominal pain in onset 1 (occurring in 3% and 1% of subjects in Fiasp (meal) and NovoRapid groups respectively, RD(95%CI): 3%(1%, 5%)). During the evaluation, it was noted that the incidence of influenza also significantly differed in the onset 1 (3% in Fiasp (post meal) and 7% in NovoRapid groups respectively, RD: -4% (-7%, -1%)). However, the incidences of both events were low and similar results were not observed in the other trials. Overall, the submission's conclusion of no meaningful differences between Fiasp and NovoRapid in treatment emergent adverse events (AEs) appears reasonable.

### ***Benefits/harms***

- 6.20 On the basis of the directly comparative evidence presented in the submission Fiasp appears to be no worse than NovoRapid when used in a bolus/basal insulin regimen or when used in CSII in the management of T1DM and T2DM in adult patients.
- 6.21 On the basis of the directly comparative evidence presented, the two preparations were also comparable with respect to frequency of adverse events.

### **Clinical claim**

- 6.22 The submission described Fiasp as non-inferior in terms of effectiveness and non-inferior in terms of safety compared to NovoRapid. Based on results from the included trials, the ESC agreed that this conclusion was reasonable for the management of T1DM and T2DM in adults. The efficacy and safety of Fiasp in children is yet to be established.
- 6.23 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.24 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

### **Economic analysis**

- 6.25 Consistent with its clinical claim of non-inferiority, the submission presented a cost-minimisation analysis comparing the daily treatment cost of Fiasp and NovoRapid. Key components and assumptions of the cost-minimisation analysis are summarised in Table 5.

**Table 5: Key components and assumptions of the cost-minimisation analysis**

| <b>Component</b>                 | <b>Claim or assumption</b>  |
|----------------------------------|---|
| Therapeutic claim: effectiveness | Based on evidence presented in the submission, effectiveness is assumed to be non-inferior. |
| Therapeutic claim: safety        | Based on evidence presented in the submission, safety is assumed to be non-inferior.        |
| Evidence base                    | Directly comparative trials of Fiasp versus NovoRapid                                       |
| Equi-effective doses             | Fiasp and NovoRapid are equi-effective on a 1:1 basis (unit to unit basis).                 |
| Direct medicine costs            | Daily costs per patient of Fiasp and NovoRapid are equivalent.                              |
| Other costs or cost offsets      | None  |

Source: Table 3.1.1, p129 of the submission.

- 6.26 An important element of the submission was the request for consideration under Section 5.7 of the Strategic Agreement 2017 between Medicines Australia and the Commonwealth of Australia (hereto referred as the Strategic Agreement) to not apply the 14.5% Statutory Price Reduction that was applied to NovoRapid on 1 June 2018 to the pricing calculations for Fiasp, however this is not a matter for PBAC and will be determined by the Minister (or delegate).
- 6.27 If treatment with Fiasp is substantially more costly than an alternative therapy or alternative therapies, the PBAC can only recommend listing of Fiasp if it is satisfied that Fiasp provides, for some patients, a significant improvement in efficacy or reduction of toxicity over these alternatives. The ESC noted that the evidence presented did not demonstrate superiority of Fiasp over alternate therapies.
- 6.28 Prices assumed for NovoRapid in the cost minimisation analysis were based on prices prior to 1 June 2018 and were higher than current DPMQs. This may not be appropriate. The usual process for evaluating a cost-minimisation analysis would be

based on non-inferiority using equi-effective doses and current published prices of listed medicines.

- 6.29 No apparent differences between Fiasp and NovoRapid were identified in the observed mean daily insulin doses for bolus and basal insulins in the included trials. On this basis, the submission appropriately claimed that at steady state, following full titration, the equi-effective doses of Fiasp to NovoRapid would be 1 unit Fiasp  $\equiv$  1 unit NovoRapid. The ESC considered the equi-effective doses proposed to be reasonable.
- 6.30 The submission assumed that as doses of basal, bolus and total insulin were equivalent for Fiasp and NovoRapid and there were no differences in the safety profiles and no difference in additional resource use would be expected. Although this was generally reasonable, it was noted that despite a similar rate of non-routine infusion set changes per 100 person years, in onset 5, significantly more patients reported non-routine changes of infusion set with Fiasp (CSII) compared with NovoRapid (CSII) (71.2% versus 57.2%). This may have any resource implications in clinical practice.
- 6.31 The submission did not perform any analysis using current PBS prices of NovoRapid (i.e., after the 1 June 2018 price reductions), which would be standard practice in cost minimisation analysis. This was conducted during the evaluation. Results are presented in Table 6 below.

**Table 6: Cost minimisation analysis using cost of NovoRapid® current as at 1 August 2018 – bolus doses**

| Component                   | Fiasp requested prices | NovoRapid® (price at 1 August 2018) |
|-----------------------------|------------------------|-------------------------------------|
| <b>T1DM</b>                 |                        |                                     |
| Cost per unit               | \$0.032                | \$0.028 <sup>^</sup>                |
| Mean daily dose, units      | 37.0                   | 37.0                                |
| Total medicine cost per day | \$1.19                 | \$1.02                              |
| Difference in cost per day  | \$0.17 extra for Fiasp |                                     |
| <b>T2DM</b>                 |                        |                                     |
| Cost per unit               | \$0.032                | \$0.028 <sup>^</sup>                |
| Mean daily dose, units      | 61.0                   | 61.0                                |
| Total medicine cost per day | \$1.96                 | \$1.68                              |
| Difference in cost per day  | \$0.28 extra for Fiasp |                                     |

<sup>^</sup> Based on current DPMQ of NovoRapid® 5x3mL cartridges (item:8435Y): \$206.59

Source: compiled during the evaluation.

- 6.32 When compared to current DPMQs of NovoRapid, treatment cost with Fiasp based on requested prices would exceed NovoRapid by \$0.17 and \$0.28 per patient per day for T1DM and T2DM respectively.

**Drug cost/patient/year:**

\$434.35 (based on estimated cost of \$1.19 per day for 365 days)

**Estimated PBS usage & financial implications**

- 6.33 This submission was not considered by DUSC. The financial estimates were reasonably based on a market share approach, assuming that Fiasp: i) would substitute for fast acting insulins (insulin aspart, insulin lispro and insulin glulisine) and ii) would not affect market growth (i.e. current growth unchanged). The model applied the assumed substitution rates of Fiasp to the total number of fast acting insulin scripts.
- 6.34 In the submission, the DPMQ for Fiasp were based on the requested DPMQs (i.e., equivalent to DPMQ of NovoRapid prior to the 14.5% statutory price reductions), whereas the DPMQ for substituted therapies (NovoRapid and insulin glulisine) were based on prices after 1 June 2018 Statutory Price Reductions. The submission also incorporated a further 5% statutory price reduction for insulin glulisine in the Year 6 estimates. During the evaluation, it was noted the applied DPMQ for Fiasp and other fast acting insulins were either incorrectly estimated or required updating to reflect the latest PBS fees. A further coding error meant cost offsets associated with reduced utilisation of the insulin glulisine vial preparation was omitted from the submission's calculations. As estimates in the base case should reflect current prices and not include future price reductions, the estimates were further amended to remove the applied 5% statutory price reduction to insulin glulisine preparations in year 6. Table 7 illustrates the estimated financial implications of the proposed listing of Fiasp after correcting for these errors and assumptions.

**Table 7: Estimated net financial implications of the proposed Fiasp listing**

|  | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 |
|--|------|------|------|------|------|------|
| <b>Estimation of use and financial impact of the proposed medicine</b>                             |      |      |      |      |      |      |
| Scripts of Fiasp   |      |      |      |      |      |      |
| Cartridges (5 x 3mL)   |      |      |      |      |      |      |
| Vials (1 x 10mL)   |      |      |      |      |      |      |
| Total  |      |      |      |      |      |      |
| Fiasp net cost to PBS/RPBS <sup>a</sup>  | \$   | \$   | \$   | \$   | \$   | \$   |
| Fiasp net cost to PBS/RPBS (net patient copay) <sup>a</sup>  | \$   | \$   | \$   | \$   | \$   | \$   |
| <b>Estimation of changes in use and financial impact of other medicines (fast acting insulins)</b> |      |      |      |      |      |      |
| Net change in units dispensed on PBS/RPBS of fast acting insulins                                  |      |      |      |      |      |      |
| NovoRapid cartridges (5 X 3mL)   |      |      |      |      |      |      |
| NovoRapid vials (1 X 10mL)   |      |      |      |      |      |      |
| Insulin lispro cartridges (5 X 3mL)  |      |      |      |      |      |      |
| Insulin lispro vials (1 X 10mL)  |      |      |      |      |      |      |
| Insulin glulisine cartridges (5 X 3mL)   |      |      |      |      |      |      |
| Insulin glulisine vials (1 X 10mL)   |      |      |      |      |      |      |
| Net cost to PBS/RPBS (net patient copay) <sup>a</sup>  |      |      |      |      |      |      |
| NovoRapid cartridges (5 X 3mL)   | \$   | \$   | \$   | \$   | \$   | \$   |
| NovoRapid vials (1 X 10mL)   | \$   | \$   | \$   | \$   | \$   | \$   |
| Insulin lispro cartridges (5 X 3mL)  | \$   | \$   | \$   | \$   | \$   | \$   |
| Insulin lispro vials (1 X 10mL)  | \$   | \$   | \$   | \$   | \$   | \$   |
| Insulin glulisine cartridges (5 X 3mL) <sup>c</sup>  | \$   | \$   | \$   | \$   | \$   | \$   |
| Insulin glulisine vials (1 X 10mL) <sup>c</sup>  | \$   | \$   | \$   | \$   | \$   | \$   |
| <b>Total</b>   | \$   | \$   | \$   | \$   | \$   | \$   |
| <b>Estimated financial implications for the PBS/RPBS</b>   |      |      |      |      |      |      |
| <b>Net cost to PBS/RPBS (net patient copayment)<sup>a</sup></b>                                    | \$   | \$   | \$   | \$   | \$   | \$   |

<sup>a</sup> updated to reflect DMPQ based on July 2018 PBS mark ups.

<sup>b</sup> Corrected for errors in the EXCEL Section 4 file: i) The DPMQs for comparators (see Table 4.1.1) ii) In the '4c. Displaced – EFF' worksheet cells C26:C27 the cost offsets for the insulin glulisine vials have not been counted.

<sup>c</sup> removed the assumed 5% statutory price reduction to insulin glulisine cartridges and vial preparation in Year 6 of listing (2024)

Source: '3a.Volumes – new', '3b.Impact – EFF', '4a.Volumes – displaced', '4b.Displaced – EFF' worksheets of Attachment 12\_Section 4\_2018\_Final file.

The redacted table shows that at Year 6 the estimated total number of scripts dispensed was 100,000 – 200,000 per year.

6.35 At year 5, the estimated net cost to the PBS was less than \$10 million.

6.36 The submission provided results of sensitivity analyses using alternate substitution rates (assuming either a 20% increase or 20% decrease in the rates). In the base case the submission assumed that substitution for NovoRapid would be at a maximum of 25% by Year 6 of listing. This was likely a significant underestimate given the similarity of Fiasp to NovoRapid. During the evaluation, a higher rate of substitution was assumed for NovoRapid preparations, starting at 20% in 2019, jumping to 60% in 2020 and increasing by 10% each year thereafter to 100% in 2024 (Y6 of listing). This increased the total estimated cost to the PBS over 6 years to \$30 - \$60 million from a base case of \$10 - \$20 million. There would still be potential for the total financial impact to further exceed this amount, as there is potential for higher substitution rates to be observed for NovoRapid more rapidly and for the rates of substitution for other fast acting insulins to exceed those assumed in the submission (starting at only

2% in Y1 increasing to 19% in Y6). The PSCR maintained that it was not expected that Fiasp would substitute for a large proportion of NovoRapid scripts, and that it was less likely that patients stable and comfortable using NovoRapid would switch to Fiasp, making the majority of expected users newly diagnosed patients as per the submission's estimated uptake rates. The PSCR also argued that the uptake rate of 20% - 100% presented in the evaluation is unlikely to occur in practice. The ESC agreed with the PSCR that an uptake rate of 100% was a likely overestimate, but considered that the estimated uptake rates presented in the submission were likely underestimated. The ESC noted that substitution may occur more rapidly than expected and that uptake would likely be between the submission and evaluation estimates. The Pre-PBAC Response stated that the lack of substitution at the pharmacy level between NovoRapid® and Fiasp would limit the uptake of Fiasp.

### ***Quality Use of Medicines***

- 6.37 The submission noted that it would be important to ensure patients switching from another insulin to Fiasp understand that Fiasp is not substitutable with other insulins at the pharmacy level. If Fiasp is substituted for other insulins, it must be done under medical supervision. Proposed quality of use medicines activities to achieve this goal include: patient and physician education, appropriate consumer medicine information, packaging and labelling to ensure patients receive proper training in the use of Fiasp. As part of the risk management actions agreed with the TGA, the sponsor will also send a letter to Health Care Professionals detailing appropriate substitution of other insulins for Fiasp, and investigate appropriate validation in prescribing and dispensing software.

### ***Financial Management – Risk Sharing Arrangements***

- 6.38 No risk sharing arrangements were proposed in the submission. However consistent with Clause 5.7.6 of the Strategic Agreement, the sponsor accepted that it may be required to enter into a Deed of Agreement reflecting the proposed staged pricing.

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of a new form of insulin aspart (Fiasp®) for the treatment of diabetes mellitus in adults on the basis of non-inferiority to the comparator NovoRapid®. The PBAC's recommendation for listing was based, among other matters, on its assessment that the cost-effectiveness of Fiasp would be acceptable if it were cost-minimised against NovoRapid on a unit for unit basis.
- 7.2 The PBAC considered that despite pharmacokinetic and pharmacodynamic differences in formulation, the listing of Fiasp on the PBS is not considered a new drug listing as insulin aspart is already PBS listed. The PBAC noted however that the two forms should be listed on the schedule as distinct PBS items to avoid inadvertent substitution or use of the alternative formulation, and considered as such that it would

not be appropriate for the brands to be treated as equivalent (the two forms should not be 'a' flagged in the schedule).

- 7.3 The PBAC agreed an unrestricted benefit listing was appropriate for Fiasp, however noted that Fiasp is not TGA registered for use in children.
- 7.4 The PBAC considered that the clinical need for Fiasp was not well established as there are a range of existing fast acting insulin products currently available on the PBS and the marginally faster time to action of Fiasp compared to other available fast acting insulins may not be clinically meaningful.
- 7.5 The PBAC agreed that NovoRapid was the appropriate comparator as Fiasp is a new formulation of an existing drug, insulin aspart, however noted that all fast acting insulins were listed on a cost-minimisation basis to each other.
- 7.6 The PBAC noted that the submission presented four head-to-head randomised control trials comparing Fiasp to NovoRapid with one of these being in Type 2 Diabetes Mellitus (T2DM) and the remaining three in Type 1 Diabetes Mellitus (T1DM). The PBAC accepted that Fiasp is non-inferior in efficacy to NovoRapid based on change from baseline of HbA1c, change from baseline in post prandial glucose, and weight gain based on the evidence presented in the submission.
- 7.7 The PBAC considered that there may be higher rates of occlusion events in infusion sets for patients using Fiasp compared to NovoRapid, and that in practice this may result in patients switching to NovoRapid to avoid further unexpected occlusions. This may result in higher expenditure due to wastage of insulin and increased use of insulin pump consumables. The PBAC was of the view that in the context of potential wastage, a small price reduction for insulin aspart may be appropriate.
- 7.8 The PBAC considered Fiasp to be non-inferior in safety to NovoRapid based on rates of hypoglycaemia events and other adverse events, based on the evidence presented in the submission.
- 7.9 The PBAC considered that the approach to the economic analysis comparing daily treatment costs to the comparator was reasonable. The PBAC noted that if treatment with Fiasp is substantially more costly than an alternative therapy or alternative therapies, the PBAC could only recommend listing of Fiasp if it is satisfied that Fiasp provides, for some patients, a significant improvement in efficacy or reduction of toxicity over these alternative fast acting insulins. As the PBAC was not satisfied that there was any improvement in efficacy with the use of Fiasp compared to the comparator, the PBAC considered that the per unit cost of Fiasp should be no higher than that of NovoRapid for it to be cost-effective.
- 7.10 The PBAC considered that the estimated uptake of Fiasp was underestimated in the submission due to the likelihood of higher substitution rates from the comparators than predicted in the submission. The PBAC agreed with the ESC that utilisation would likely fall between the submission's estimate of 25% substitution at year 6 and

evaluation estimate of 100% substitution at year 6.

- 7.11 The PBAC recommend that insulin aspart should be treated as interchangeable on an individual patient basis with insulin lispro and insulin glulisine.
- 7.12 The PBAC advised that Fiasp is suitable for prescribing by nurse practitioners.
- 7.13 The PBAC recommended that the Early Supply Rule should apply.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Add new item:

| Name, Restriction,<br>Manner of administration and form  | Max.<br>Qty | No. of<br>Rpts | Proprietary Name and Manufacturer |              |
|--|-------------|----------------|-----------------------------------|--------------|
| INSULIN ASPART<br>100 units/mL injection (fast acting) solution,<br>1 x 10 mL vial             | 5           | 2              | Fiasp®                            | Novo Nordisk |
| INSULIN ASPART<br>100 units/mL injection (fast acting) solution,<br>5 x 3 mL cartridges        | 5           | 1              | Fiasp<br>Penfill®                 | Novo Nordisk |
| INSULIN ASPART<br>100 units/mL injection (fast acting) solution,<br>5 x 3 mL injection devices | 5           | 1              | Fiasp<br>FlexTouch®               | Novo Nordisk |

|                                    |   |
|------------------------------------|---|
| <b>Category / Program</b>          | GENERAL – General Schedule (Code GE)  |
| <b>Prescriber type:</b>            | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists<br><input type="checkbox"/> Midwives  |
| <b>Restriction Level / Method:</b> | <input checked="" type="checkbox"/> Unrestricted<br><input type="checkbox"/> Restricted benefit<br><input type="checkbox"/> Authority Required - In Writing<br><input type="checkbox"/> Authority Required - Telephone<br><input type="checkbox"/> Authority Required - Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input type="checkbox"/> Streamlined |

## **9 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **10 Sponsor's Comment**

Novo Nordisk is pleased that a faster acting insulin alternative will be made available to patients on the PBS.