5.21 SEMAGLUTIDE, Solution for injection 2 mg in 3 mL pre-filled pen, Ozempic®, Novo Nordisk Pharmaceuticals Pty. Limited

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule Authority Required (Telephone/Online) listing of a new strength of semaglutide for initial treatment and an Authority Required (STREAMLINED) listing for continuing treatment of type 2 diabetes mellitus (T2DM).

1.2 The submission advised that in addition to the request to list the semaglutide 3 mg in 3 mL (0.68 mg/mL) injection on the PBS, the sponsor intends to discontinue the existing 2 mg in 1.5 mL pre-filled pen. The sponsor submitted a separate delisting request.

1.3 Listing was requested based on a cost-minimisation approach for the semaglutide 2 mg in 3 mL pre-filled injector pen versus semaglutide 2 mg in 1.5 mL pre-filled injector pen.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Insufficiently controlled type 2 diabetes mellitus (T2DM)
Intervention	Semaglutide 2 mg in 3.0 mL in prefilled injector pen (0.68 mg/mL injection)
Comparator	Semaglutide 2 mg in 1.5 mL in prefilled injector pen (1.34 mg/mL injection)
Outcomes	Bioequivalence, and non-inferior device performance and safety
Clinical claim	Non-inferiority

Source: Table 1-1, p 10 of the submission main body.

2 Background

Registration status

2.1 **TGA status at time of PBAC consideration:** The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA Delegate's Overview was available. The PBAC noted that the TGA Delegate proposed to approve registration of the product.

Previous PBAC consideration

2.2 Submissions requesting the listing of semaglutide on the PBS for the treatment of T2DM were considered at the November 2019 and March 2020 meetings and listing occurred on 1 July 2020. A submission to request extension of the listing to include treatment in combination with insulin was recommended in March 2021.

2.3 On 1 June 2024, changes were made to the restrictions for semaglutide to implement recommendations made by the PBAC in July 2023. The main changes were:

- The authority type for therapy initiation for all indications was changed from Authority Required (STREAMLINED) to Authority Required (telephone/electronic), continuing access remains via an Authority Required (STREAMLINED) restriction.
- Patients must be contraindicated, intolerant, or must not have achieved a clinically meaningful glycaemic response to a sodium-glucose cotransporter 2 (SGLT2) inhibitor to initiate PBS-subsidised semaglutide therapy.

3 Requested listing

3.1 The submission proposed to list semaglutide 2 mg in 3 mL pre-filled pen under the same circumstances as the existing PBS-listed 2 mg in 1.5 mL pre-filled pen presentation for the treatment of T2DM. This includes an Authority Required (Telephone/Online) listing for therapy initiation and an Authority Required (STREAMLINED) restriction for continuing treatment (PBS item code 14149Q).

3.2 The submission did not request any change to the current effective price of semaglutide.

MEDICINAL PRODUCT **medicinal product pack**	Dispensed Price for Max. Qty	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
SEMAGLUTIDE					
semaglutide 0.68 mg/mL injection, 3 mL pen device	$134.27 published price $ [redacted] effective price	1	1	5	Ozempic
Category / Program: General Schedule					
Prescriber type: ☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐					
Restriction type: Authority Required (telephone/online PBS Authorities system)					
Indication: Diabetes mellitus type 2					
Treatment Phase: First PBS-prescription for this drug					
Clinical criteria:					
The treatment must be used in combination with at least one of: metformin, a sulfonylurea, insulin,					
AND					
Clinical criteria:					
The condition must be inadequately responsive to at least one of: metformin, a sulfonylurea, insulin,					
AND					
Clinical criteria:					
Patient must not have achieved a clinically meaningful glycaemic response with an SGLT2 inhibitor; OR					
Patient must have a contraindication/intolerance requiring treatment discontinuation of an SGLT2 inhibitor.					
Treatment criteria:					
Patient must not be undergoing concomitant PBS-subsidised treatment for type 2 diabetes mellitus with any of: an SGLT2 inhibitor, a DPP4 inhibitor, another GLP-1 receptor agonist.					
Administrative Advice: Abbreviations used in the restriction are as follows: SGLT2 – sodium glucose transporter-2 inhibitor (drug names ending in 'flozin') DPP4 – dipeptidyl peptidase-4 inhibitor (drug names ending in 'gliptin') GLP-1 – glucagon-like peptide-1 receptor agonist					

Administrative Advice: Where an SGLT2 inhibitor is being accessed through a PBS indication other than diabetes, the clinical criterion excluding concomitant treatment with an SGLT2 inhibitor is in relation to diabetes mellitus type 2 only.
Administrative Advice: Definition: A HbA1c measurement greater than 7% despite treatment with the specified prior therapy/therapies indicates inadequate responsiveness. Where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2-week period indicates inadequate responsiveness. Blood glucose monitoring is an alternative to HbA1c measurement where at least one of the following circumstances applies: (a) A clinical condition with reduced red blood cell survival (inclusive of haemolytic anaemias, haemoglobinopathies), (b) Red cell transfusion within the previous 3 months. Document HbA1c measurements (blood glucose measurements where relevant), as well as any intolerances/contra-indications in the patient's medical records.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Administrative Advice: Special Pricing Arrangements apply.
Category / Program: General Schedule
Prescriber type: ☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐
Restriction type: Authority Required (STREAMLINED)
Indication: Diabetes mellitus type 2
Treatment Phase: Subsequent PBS-prescriptions for any GLP-1 receptor agonist
Treatment criteria:
Patient must not be undergoing concomitant PBS-subsidised treatment for type 2 diabetes mellitus with any of: an SGLT2 inhibitor, a DPP4 inhibitor, another GLP-1 receptor agonist.
Administrative Advice: Abbreviations used in the restriction are as follows: SGLT2 – sodium glucose transporter-2 inhibitor (drug names ending in 'flozin') DPP4 – dipeptidyl peptidase-4 inhibitor (drug names ending in 'gliptin') GLP-1 – glucagon-like peptide-1 receptor agonist
Administrative Advice: Where an SGLT2 inhibitor is being accessed through a PBS indication other than diabetes, the clinical criterion excluding concomitant treatment with an SGLT2 inhibitor is in relation to diabetes mellitus type 2 only.
Administrative Advice: Special Pricing Arrangements apply.

4 Population and disease

4.1 The target population for the new semaglutide 2 mg in 3 mL in pre-filled injector is identical to the existing PBS-listed 2 mg in 1.5 mL pre-filled pen.

4.2 The submission stated that the proposed listing is not expected to change the clinical management of T2DM and therefore did not present a detailed clinical management algorithm.

5 Comparator

5.1 The submission nominated the currently PBS-listed semaglutide 2 mg in 1.5 mL (1.34 mg/mL) in a pre-filled pen presentation as the comparator. This is appropriate. The evaluation noted that the PBAC has previously accepted dulaglutide 1.5 mg as a comparator (Para 7.2 Semaglutide Public Summary Document March 2021 PBAC meeting).

5.2 The submission noted that the proposed semaglutide 2 mg in 3 mL presentation would replace the current PBS-listed semaglutide 2 mg in 1.5 mL presentation, which is being discontinued.

6 Consideration of evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (5) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with semaglutide including reduced glycaemic variability, weight loss, and quality of life benefits including increased ability to work and provide care for family members. One individual requested PBS subsidisation of semaglutide for the treatment of hyperinsulinemia; one requested access to the 8 mg in 3 mL pen device for patients with T2DM; and one raised the issue of lack of subsidised access to semaglutide for patients with HbA1c <7% who have high glycaemic variability. Individuals noted mild gastrointestinal side effects and issues with accessing the medication due to shortages.

Clinical studies

6.3 The submission was based on a cross-trial indirect comparison of outcomes from two pharmacokinetic bioequivalence studies comparing different concentrations of semaglutide at a dose of 0.25 mg delivered subcutaneously (Studies 4649 and 4387). Study 4649 compared semaglutide 0.68 mg/mL to 1.0 mg/mL, both delivered via the PDS290 pen injector. Study 4387 compared the approved semaglutide product concentration of 1.34 mg/mL delivered via the PDS290 pen injector to a 0.5 mg/mL formulation delivered via the DV3372 pen injector.

6.4 A cross-trial comparison between semaglutide 0.68 mg/mL in Study 4649 and the currently approved concentration of semaglutide 1.34 mg/mL in Study 4387 was formally pre-specified in the Study 4649 analysis plan prior to the database lock.

6.5 Details of the studies presented in the submission are provided in Table 2.

Table 2: Pharmacokinetic bioequivalence studies presented in the submission

Trial ID	Protocol title	Publication citation
Study 4649 NCT04228354	A trial to demonstrate bioequivalence between semaglutide drug product concentrations 0.68 mg/mL and 1.0 mg/mL. CSR: 28 October 2021.	NR
Study 4387 NCT03598621	A Trial to Demonstrate Bioequivalence Between Semaglutide Formulations for the DV3372 device and the Formulation for the PDS290 Semaglutide Pen-injector. CSR: 21 May 2019.	NR

Source: Table 2-1, p 14 of the submission main body. NR = Not reported.

6.6 The key features of the studies are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Semaglutide 0.68 mg/mL vs 1.0 mg/mL					
Study 4649	28	R, DB, SC, XO 5 weeks	Low	Male or female, 18-55 years, BMI 20.0-27.0 kg/m^2	$AUC_{0\text{-}tz}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, $t_{1/2}$, Cl/F, Vz/F, adverse events
Semaglutide 1.34 mg/mL (PDS290 pen injector) vs 0.5 mg/mL (DV3372 pen injector)					
Study 4387	24	R, DB, SC, XO 5 weeks	Low	Healthy, male or female, 18-55 years, BMI 20.0-29.9 kg/m^2	$AUC_{0\text{-}tz}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, $t_{1/2}$, Cl/F, Vz/F, adverse events

Source: p17-19, 22, 24 of the submission main body.

Abbreviations: $AUC_{0\text{-}tz}$ = area under plasma concentration curve from time 0 until time of last quantifiable measurement; $AUC_{0\text{-}inf}$ = area under curve at infinite time; BMI = body mass index; Cl/F = total apparent clearance; C_{max} = maximum plasma concentration; DB = double blind; SC = Single centre; T_{max} = time to C_{max}; $t_{1/2}$ = terminal elimination half-life; R = randomised; Vz/F = apparent volume of distribution; XO = crossover.

Note: Duration is given as time followed after single dose.

Comparative effectiveness

6.7 The PBAC noted the evidence submitted in support of the claim of bioequivalence between the existing PBS listed semaglutide 2 mg in 1.5 mL prefilled pen and the 2 mg in 3 mL prefilled pen. The PBAC noted the TGA Delegate's advice that the cross-trial comparison using data from trial 4649 (0.25 mg dose at drug product concentration 0.68 mg/mL) and trial 4387 (0.25 mg dose at drug product concentration 1.34 mg/mL) showed comparable pharmacokinetic profiles between the two concentrations, supporting a change in subcutaneous semaglutide concentration from 1.34 mg/mL to 0.68 mg/mL for PDS290 pen-injector.

Comparative harms

6.8 The PBAC noted the data submitted to support the claim of non-inferior safety of the existing PBS listed semaglutide 2 mg in 1.5 mL prefilled pen and the 2 mg in 3 mL prefilled pen. The PBAC noted the TGA Delegate's advice that the safety profile of semaglutide observed in Study 4649 and 4387 is consistent with the known safety profile of subcutaneous semaglutide and that no new safety signals were observed.

6.9 No extended assessment of comparative harms was presented by the submission; the submission stated that given the established PBS listing for semaglutide and the simple nature of the proposed substation of dose forms, no extended analysis of comparative harms was conducted. This was reasonable, noting semaglutide has been PBS listed since 1 July 2020.

Clinical claim

6.10 The submission described the semaglutide 0.68 mg/mL concentration as bioequivalent to the 1.34 mg/mL concentration. The submission noted that the PDS290 pen injector with 3.0 mL cartridge is already TGA-approved for administration of the 1.0 mg maintenance dose.

Interpretation of clinical evidence

6.11 The PBAC considered that the claims of bioequivalence and non-inferior safety to semaglutide 1.34 mg/mL were reasonable.

Economic analysis

6.12 The submission presented a cost-minimisation approach versus the current PBS-listed 2 mg in 1.5 mL (1.34 mg/mL) pre-filled pen. The approach was based on drug costs only and no other resource costs were identified by the submission.

6.13 The equi-effective doses used for the analysis were semaglutide 2 mg in 3 mL (0.68 mg/mL) pen device = semaglutide 2 mg in 1.5 mL (1.34 mg/mL) pen device.

Estimated PBS usage & financial implications

6.14 The submission used a market share approach to estimate the financial impact of substituting the new semaglutide 2 mg in 3 mL pen device for the current PBS-listed 2 mg in 1.5 mL pen device and estimated this change to be cost neutral to the PBS and Australian Government health budget. The submission assumed no changes to current clinical practice.

6.15 The submission proposed no change to the published or effective price for semaglutide (published DMPQ for semaglutide for the 1.5 mL pen injector at 1 June 2024: $134.27) and assumed no change in treatment uptake, compliance, adherence, or setting of care. The costings provided in the submission were calculated using the published DPMQ.

6.16 Key inputs for the financial estimates are shown in Table 4.

Table 4: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Market size	Based on Services Australia data for PBS item 10280T (semaglutide 1.34 mg/mL in 1.5 mL) for 2023 calendar year. Assumes a 13:1 split for initial and continuing therapy scripts, noting that the restrictions were changed in June 2024, so there are no data available to inform this assumption. Assumes a declining growth rate of 5% in Year 1 to 0% in Year 6, due to the 1 June 2024 PBS restriction changes.	The new semaglutide 2 mg in 3 mL pen device is not expected to grow the eligible patient population.

Source: Section 4, p 41 of the submission main body main.

6.17 The estimated number of prescriptions and financial implications of the listing are shown in Table 5.

Table 5: Estimated use and financial implications based on published prices

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of semaglutide 0.68 mg/mL in 3 mL pen device						
Cost to PBS/RPBS less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Estimated financial implications for semaglutide 1.34 mg/mL in 1.5 mL pen device						
Cost to PBS/RPBS less copayments	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net financial implications						
Net cost to PBS/RPBS	$0	$0	$0	$0	$0	$0

Source: Table 4-1 to 4-4, pp 42-44 of the submission.

The redacted values correspond to the following ranges:

[1] *900,000 to < 1,000,000*

[2] *1,000,000 to < 2,000,000*

[3] *$100 million to < $200 million*

[4] *net cost saving*

6.18 The submission stated that the 2 mg in 3 mL pen device is being introduced to increase production efficiency to address product shortages, and that the currently listed 2 mg in 1.5 mL pen device is being discontinued. Overall, the semaglutide 2 mg in 3 mL pen device would not be expected to grow the eligible population. The proposed listing would be expected to have nil cost to the PBS/RPBS, provided 2 mg in 1.5 mL pen device is discontinued.

6.19 At year 6, the estimated net cost to the PBS/RPBS would be $0.

7 PBAC Outcome

7.1 The PBAC recommended the listing of semaglutide 2 mg in 3 mL pre-filled pen on the PBS General Schedule for the treatment of T2DM as an Authority Required (Telephone/Online) listing for initial treatment and an Authority Required (STREAMLINED) listing for continuing treatment, under the same conditions as the currently listed 2 mg in 1.5 mL pre-filled pen. The PBAC's recommendation for listing was based on, among other matters, its assessment that semaglutide 2 mg in 3 mL would be cost-effective if it was cost-minimised against semaglutide 2 mg in 1.5 mL.

7.2 The PBAC considered that the equi-effective doses were semaglutide 2 mg in 3 mL (0.68 mg/mL) pen device = semaglutide 2 mg in 1.5 mL (1.34 mg/mL) pen device.

7.3 The PBAC noted the sponsor's intention to delist semaglutide 2 mg in 1.5 mL once semaglutide 2 mg in 3 mL is listed on the PBS.

7.4 The PBAC considered that the nominated comparator of semaglutide 2 mg in 1.5 mL pre-filled pen was reasonable.

7.5 The PBAC considered that the claims of bioequivalence and non-inferior safety were reasonable. The PBAC noted the TGA Delegate's advice that based on the pharmacokinetic data submitted bioequivalence was demonstrated between subcutaneous semaglutide concentration 1.34 mg/mL (2 mg in 1.5 mL pre-filled pen)

and 0.68 mg/mL (2 mg in 3 mL pre-filled pen). The PBAC also noted the TGA Delegate's advice that the safety profile of semaglutide observed in the data submitted was consistent with the known safety profile of subcutaneous semaglutide and that no new safety signals were observed.

7.6 The PBAC considered that the listing of semaglutide 2 mg in 3 mL would not result in a net cost to the PBS.

7.7 The PBAC advised that semaglutide 2 mg in 3 mL is suitable for prescribing by nurse practitioners.

7.8 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because semaglutide 2 mg in 3 mL is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over semaglutide 2 mg in 1.5 mL, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.9 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**No. of repeats**	**Available brands**
SEMAGLUTIDE					
semaglutide 1.34 mg/mL injection, 1 x 1.5 mL pen device	12080T MP NP	1	1	5	Ozempic
semaglutide 0.68 mg/mL injection, 1 x 3 mL pen device	*NEW MP NP*	*1*	*1*	*5*	*Ozempic*
Restriction Summary / Treatment of Concept:					
	Category / Program: GENERAL – General Schedule (GE)				
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners				
	Restriction type: Authority Required (telephone/online PBS Authorities system)				
	Administrative Advice: Special Pricing Arrangements apply.				
	Indication: Diabetes mellitus type 2				
	Treatment Phase: First PBS-prescription for this drug				
	Clinical criteria:				
	The treatment must be used in combination with at least one of: metformin, a sulfonylurea, insulin.				
	AND				
	Clinical criteria:				

	The condition must be inadequately responsive to at least one of: metformin, a sulfonylurea, insulin,
	AND
	Clinical criteria:
	Patient must not have achieved a clinically meaningful glycaemic response with an SGLT2 inhibitor; or
	Patient must have a contraindication/intolerance requiring treatment discontinuation of an SGLT2 inhibitor.
	Treatment criteria:
	Patient must not be undergoing concomitant PBS-subsidised treatment for type 2 diabetes mellitus with any of: an SGLT2 inhibitor, a DPP4 inhibitor, another GLP-1 receptor agonist.
	Administrative Advice: Abbreviations used in the restriction are as follows: SGLT2 – sodium glucose co-transporter-2 inhibitor (drug names ending in 'flozin') DPP4 – dipeptidyl peptidase-4 inhibitor (drug names ending in 'gliptin') GLP-1 – glucagon-like peptide-1 receptor agonist
	Administrative Advice: Where an SGLT2 inhibitor is being accessed through a PBS indication other than diabetes, the clinical criterion excluding concomitant treatment with an SGLT2 inhibitor is in relation to diabetes mellitus type 2 only.
	Administrative Advice: Definition: A HbA1c measurement greater than 7% despite treatment with the specified prior therapy/therapies indicates inadequate responsiveness. Where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2-week period indicates inadequate responsiveness. Blood glucose monitoring is an alternative to HbA1c measurement where at least one of the following circumstances applies: (a) A clinical condition with reduced red blood cell survival (inclusive of haemolytic anaemias, haemoglobinopathies), (b) Red cell transfusion within the previous 3 months. Document HbA1c measurements (blood glucose measurements where relevant), as well as any intolerances/contra-indications in the patient's medical records.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
SEMAGLUTIDE					
semaglutide 1.34 mg/mL injection, 1 x 1.5 mL pen device	14149Q MP NP	1	1	5	Ozempic
semaglutide 0.68 mg/mL injection, 1 x 3 mL pen device	*NEW* *MP NP*	*1*	*1*	*5*	*Ozempic*
Restriction Summary / Treatment of Concept:					
	Category / Program: GENERAL – General Schedule (GE)				
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners				
	Restriction type: ☒Authority Required (STREAMLINED)				
	Administrative Advice: Special Pricing Arrangements apply.				

	Indication: Diabetes mellitus type 2
	Treatment Phase: Subsequent PBS-prescriptions for any GLP-1 receptor agonist
	Treatment criteria:
	Patient must not be undergoing concomitant PBS-subsidised treatment for type 2 diabetes mellitus with any of: an SGLT2 inhibitor, a DPP4 inhibitor, another GLP-1 receptor agonist.
	Administrative Advice: Abbreviations used in the restriction are as follows: SGLT2 – sodium glucose co-transporter-2 inhibitor (drug names ending in 'flozin') DPP4 – dipeptidyl peptidase-4 inhibitor (drug names ending in 'gliptin') GLP-1 – glucagon-like peptide-1 receptor agonist
	Administrative Advice: Where an SGLT2 inhibitor is being accessed through a PBS indication other than diabetes, the clinical criterion excluding concomitant treatment with an SGLT2 inhibitor is in relation to diabetes mellitus type 2 only.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.