5.19 INSULIN GLARGINE
Injections (human analogue), cartridges, 100 units per mL, 3 mL, 5,
Semglee®, Alphapharm Pty Ltd

1 Purpose of Application

1.1 The minor submission sought listing for a biosimilar brand of insulin glargine (Semglee®), on the General Schedule (Section 85) as an unrestricted benefit.

2 Background

2.1 The Semglee® brand of insulin glargine was TGA registered on 28 March 2018.

2.2 The PBAC has not previously considered an application for this brand of insulin glargine.

2.3 There are three PBS-listed presentations of the reference product, Lantus: vials for injection, cartridges for use in reusable injection pens and pre-filled disposable pen devices. The pre-filled disposable pen presentation, known as Lantus SoloStar®, is the same presentation as Semglee®. The sponsor has proposed that Semglee® be 'a' flagged to Lantus SoloStar® but not to the other presentations of Lantus.

2.4 At its March 2015 meeting, the PBAC recommended the listing of Basaglar®, a biosimilar brand of insulin glargine, on a cost-minimisation basis with its reference product, Lantus. The PBAC also recommended that Basaglar and Lantus cartridge presentations could be 'a' flagged to each other, and the Basaglar KwikPen and Lantus SoloStar pre-filled disposable pens could be 'a' flagged to each other. During the PBAC evaluation, the sponsor raised concerns regarding the safety of substitution and potential risks to pharmacovigilance. The PBAC noted these concerns but is satisfied regarding the safety of substitution as it is performed in consultation with, and with the consent of, the patient. The PBAC was also of the view that education and promotion regarding biosimilars was an opportunity to enhance pharmacovigilance by pharmacists (insulin glargine public summary document, November 2015). To date, Basaglar has not progressed to PBS listing.

Brand equivalence and substitution at the pharmacist level ('a' flagging)

2.5 The Schedule of Pharmaceutical Benefits provide the following definition of brand equivalence:

Extract from the Explanatory Notes to the PBS Schedule[1]

BRAND EQUIVALENCE

'a' located immediately before brand names of a particular strength of an item indicates that the sponsors of these brands have submitted evidence that they have been demonstrated to be bioequivalent or therapeutically equivalent, or that justification for not needing bioequivalence or therapeutic equivalence data has been provided to and accepted by the Therapeutic Goods Administration. It would thus be expected that these brands may be interchanged without differences in clinical effect.

2.6 Many medicines are available on the PBS in different brands. The Schedule of Pharmaceutical Benefits indicates where different brands are considered equivalent for the purposes of substitution at the point of dispensing by using 'a' flags.

2.7 The ability for prescribers and pharmacists to substitute generic or biosimilar brands for originator brands is an important part of encouraging use of generics and biosimilars in the marketplace and adds to the sustainability of the PBS.

2.8 For any individual prescription, a prescriber may choose to not permit brand substitution by indicating 'substitution not permitted' on the prescription. Likewise, when substitution is permitted, a patient may nominate which 'a' flagged brand they wish to receive from the pharmacist, except when State or Territory Law prohibits substitution (e.g. for Schedule 8 drugs of dependence). The substitution process allows for patient and prescriber choice and is not automatic.

2.9 The *National Health Act* 1953 ("The Act") makes it an offence for a pharmacist to supply a pharmaceutical benefit other than the benefit directed to be supplied in a prescription except when, amongst other criteria, the Schedule issued by the Department of Health states that the specified benefit and the substitute benefit are equivalent.

2.10 At the March 2018 meeting, the PBAC advised that the following revised considerations will be used to make a recommendation on brand equivalence ('a' flagged) of biosimilars with the reference brand;

- The Therapeutic Goods Administration has determined that the product is a biosimilar of the reference medicine as evidenced by ARTG registration documentation;
- Availability of supportive data relating to the effects of switching between the reference product and the biosimilar product/s; and
- Practical considerations relating to substitution by the pharmacist at the point of dispensing. This includes strength of formulation, number of units per pack and

[1] Symbols used in the Schedule - http://www.pbs.gov.au/info/healthpro/explanatory-notes/section2/section-2-symbols

maximum quantities between the brands, which may make substitution at the pharmacy level difficult from a practical perspective.

2.11 The PBAC considered that where a biosimilar product could not be recommended to be brand equivalent ('a' flagged) at the time of PBS listing, data should be collected to support this consideration at a later point.

2.12 If the PBAC provides advice on brand equivalence ('a' flagging), the decision to apply brand equivalence to listings in the Schedule is made by the Minister for Health (or Delegate).

Biosimilar uptake measures

2.13 The biosimilar uptake measures were agreed as part of the strategic agreements that the Government reached with Medicines Australia, the Generic and Biosimilar Medicines Association and the Pharmacy Guild of Australia as part of the 2017 Budget process.

2.14 The PBAC will advise whether implementation of the uptake drivers is likely to raise any clinical or other concerns about appropriate use on the PBS. The PBAC may, on a case-by-case basis, provide advice relating to:

- encouraging the prescribing of a biosimilar brand for treatment naïve patients; and
- applying a lower level of authority to biosimilar brand(s) than exists for the reference brand of biological medicines.

2.15 After PBAC advice is received, a decision will be made about applying the drivers for the relevant medicine. The policy provides for lower authority requirements only for biosimilar brands, but there will be no increase in authority requirements to prescribe reference brands.

2.16 The PBAC has previously stated it had no concerns about encouraging prescribing of a biosimilar brand rather than the reference biological agent brand for treatment naïve patients, including through notes in the Schedule and prescribing software changes. (Etanercept (Brenzys) Public Summary Document, August 2017 PBAC Meeting).

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Requested listing

3.1 The submission requested, with the exception of the price, an identical listing to the currently listed PBS reference brand Lantus®.

3.2 The submission requested Semglee® be 'a' flagged with the pre-filled disposable pen presentation of Lantus, Lantus SoloStar.

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

Name, restriction, manner of administration, form	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity (DPMQ)	Proprietary name and manufacturer
INSULIN GLARGINE ~~Semglee® (insulin glargine),~~ ~~100 IU /mL, 3 mL, Type 1, colourless glass cartridges inside pre-filled, disposable pen devices~~ *insulin glargine 100 units/mL injection, 5 x 3 mL cartridges*	5	1	$[redacted]	Semglee, Alphapharm Pty Ltd
Administrative instructions	***Note*** ***Biosimilar prescribing policy*** *Prescribing of the biosimilar brand SEMGLEE® is encouraged for treatment naive patients.* *Encouraging biosimilar prescribing for treatment naive patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the Biosimilar Awareness Initiative webpage (www.health.gov.au/biosimilars).*			

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Comparator

4.1 The minor submission nominated the reference brand of insulin glargine (Lantus) as the comparator.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

5.3 The minor submission outlined the studies required by the TGA in determining comparability between the biosimilar and reference brands of insulin glargine. There were three key clinical studies, of which the submission presented two pivotal studies that demonstrated clinical comparability between Semglee® and Lantus; INSTRIDE 1 and INSTRIDE 2.

Table 1: Trials and associated reports presented in the re-submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
INSTRIDE 1 MYL-GAI-3001 CTRI/EUDRACT 2014-000747-32	An Open-label, Randomized, Multi-centre, Parallel-group Clinical Trial Comparing the Efficacy and Safety of Mylan's Insulin glargine with Lantus® in Type 1 Diabetes Mellitus Patients.	NA
INSTRIDE 2 MYL-GAI-3002 EUDRACT No. 2014-000881-23	An Open-label, Randomized, Multicentre, Parallel-Group Clinical Trial Comparing the Efficacy and Safety of Mylan's Insulin Glargine with Lantus® in Type 2 Diabetes Mellitus Patients.	NA

Source: Minor submission, pg 19-20

5.4 The minor submission presented results of both studies in a summarised form and the complete Clinical Study Reports for both trials were provided as attachments to the submission.

Comparative effectiveness and comparative harms

5.5 The submission claimed that the results of the clinical trials showed that Semglee® was non-inferior to Lantus in terms of efficacy and safety.

5.6 The sponsor was requested to provide a copy of the TGA clinical evaluation report (CER) on Semglee, which concluded that:

- the evidence of pharmacokinetic bioequivalence of the biosimilar product with the original Lantus formulation of insulin glargine appeared conclusive;
- bioequivalence between the biosimilar product and the reference product Lantus was clearly shown on pharmacodynamic grounds;
- the submitted data provided adequate evidence of efficacy in all aspects of the stated indication; and
- the submission contained a substantial body of evidence that use of the new biosimilar glargine product was not associated with any newly emerging safety risk, nor any greater incidence of adverse effects, than was experienced with the existing registered product.
- the CER noted that there was no data on use in children, but ultimately found that it was reasonable to extrapolate efficacy in children from the adult data on Semglee® and the paediatric data on Lantus (section 11.1 of the CER).

5.7 This submission did not require further consideration by the Advisory Committee on Medicines (ACM).

5.8 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

5.9 The PBAC considered that the claim of non-inferior safety was reasonable.

Financial implications

5.10 If recommended, Semglee® would be the first biosimilar brand of insulin glargine to be listed on the PBS. Under the latest amendments to the *National Health Act 1953* the maximum statutory reduction for first new brands of a pharmaceutical item from 1 October 2018 is 25%.

5.11 The Sponsor proposed an ex-manufacturer price for Semglee® of 305.87, which is 25% lower than the price of Lantus at the time of submission ($360.75). The Secretariat noted that a 25% price reduction to the published DPMQ of Lantus ($406.25) is $304.69. In its pre-PBAC response, the sponsor clarified that it wished to propose an ex-manufacturer price of $270.55, which is 25% lower than the price of Lantus at the time of the submission ($360.75) and with standard fees and mark-ups results in a DPMQ for Semglee® of $305.87.

5.12 The minor submission estimated a net save to the PBS of $10 - $20 million in Year 6 of listing with a total net save to the PBS/RPBS of $30 - $60 million over the first 6 years in listing. This is summarised in the redacted table below.

Table 2: Estimated net cost to the PBS/RPBS for Semglee

	2018	2019	2020	2021	2022	2023
Projected net cost of new listing (Semglee)						
to PBS	$	$	$	$	$	$
to RPBS	$	$	$	$	$	$
to PBS/RPBS	$	$	$	$	$	$
Projected net savings of displaced medicines (Lantus)						
to PBS	-$	-$	-$	-$	-$	-$
to RPBS	-$	-$	-$	-$	-$	-$
to PBS/RPBS	-$	-$	-$	-$	-$	-$
Net cost to the PBS/RPBS						
to PBS	-$	-$	-$	-$	-$	-$
to RPBS	-$	-$	-$	-$	-$	-$
to PBS/RPBS	-$	-$	-$	-$	-$	-$
Projected net cost of Lantus not replaced with Semglee® (after 25% price cut)						
to PBS	-$	-$	-$	-$	-$	-$
to RPBS	-$	-$	-$	-$	-$	-$
to PBS/RPBS	-$	-$	-$	-$	-$	-$
Overall net cost to the PBS/RPBS						
to PBS	-$	-$	-$	-$	-$	-$
to RPBS	-$	-$	-$	-$	-$	-$
to PBS/RPBS	**-$**	**-$**	**-$**	**-$**	**-$**	**-$**

Source: Minor submission, pg 50

5.13 The sponsor acknowledged that at the time of the submission a special pricing

arrangement applied to Lantus, and using the effective price would affect the forward estimates.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC recommended listing the biosimilar brand of insulin glargine (Semglee) on the General Schedule (Section 85) as an unrestricted benefit.

6.2 In making this recommendation, the PBAC noted the TGA CER on Semglee® concluded that the TGA was satisfied that Semglee® was bioequivalent to the reference product, Lantus and was non-inferior in terms of both efficacy and safety.

6.3 The PBAC advised that, under Section 101(4AACD) of the *National Health Act 1953*, the Semglee® and Lantus Solostar brands of insulin glargine Injections (human analogue), cartridges, could be marked as equivalent in the Schedule of Pharmaceutical Benefits for the purposes of substitution at the pharmacy level.

6.4 The PBAC considered that health care professionals could safely manage any differences in the devices in the course of regular patient education and counselling they provide on the use of devices.

6.5 The PBAC noted that the Special Pricing Arrangement for Lantus and Lantus Solostar was removed from 1 June 2018, and the current price in the Schedule of Pharmaceutical Products for these brands of insulin glargine is $240.29 DPMQ ($211.40 ex-man). For the savings to be realised as presented in the submission, the reduction proposed by the sponsor would need to be calculated from this price.

6.6 The PBAC advised that there are no clinical or other concerns about appropriate use of medicines, if the policy decision were made to apply the following uptake driver to the proposed indication:

- Encouraging the prescribing of a biosimilar brand for treatment naïve patients.

6.7 The PBAC noted that the following uptake driver was not appropriate, as the reference product is currently an unrestricted benefit.

- Applying a lower level of authority to biosimilar brand(s) than exists for the reference brand of biological medicines.

6.8 The PBAC considered that the Australian Government be requested, through the Biosimilar Education Grant, to support the PBS listing of the first insulin biosimilar in the diabetic setting via the development of educational materials aimed at consumers and health care professionals.

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

Outcome:
Recommended

7 Recommended listing

7.1 Add new item:

Name, restriction, manner of administration, form	Maximum quantity (units)	No. of repeats	Proprietary name and manufacturer
INSULIN GLARGINE insulin glargine 100 units/mL injection, 5 x 3 mL cartridges	5	1	Semglee, Alphapharm Pty Ltd
Administrative Advice	**Note** **Biosimilar prescribing policy** Prescribing of the biosimilar brand SEMGLEE® is encouraged for treatment naive patients. Encouraging biosimilar prescribing for treatment naive patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the Biosimilar Awareness Initiative webpage (www.health.gov.au/biosimilars).		

8 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.

9 Sponsor's Comment

Alphapharm welcomes the PBAC's decision to recommend Semglee for Australian patients and looks forward to a PBS listing at the earliest opportunity.