5.31 INSULIN GLARGINE 3 mL cartridges, 100 IU/mL; Basaglar®; Eli Lilly.

1 Purpose of Application

1.1 The PBAC was requested to consider:

a. The unrestricted benefit listing of insulin glargine (Basaglar®), a biosimilar of the PBS-listed insulin glargine, Lantus®.
b. The marking as equivalent (i.e. "a" flagging) in the Schedule of Pharmaceutical Benefits (the Schedule) of the insulin glargine products, Basaglar and Lantus.

1.2 Note: the sponsor's submission did not request an "a" flag. The Minister (delegate) had requested PBAC to provide advice on this matter under section 101(3) of the *National Health Act 1953* (the Act). The advice is not being published at this stage.

2 Requested listing

2.1 The submission requested the following new listing:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
INSULIN GLARGINE Insulin glargine 100 international units/mL injection, 5 x 3 mL cartridges	5	1	$[redacted]#	Basaglar* Basaglar* KwikPen	Eli Lilly

*Trade name was previously Abasria®

[redacted]

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☒Medical Practitioners ☒Nurse practitioners

3 Background

3.1 The following information is outlined below:

- TGA consideration of Basaglar
- PBS history of insulin glargine and other insulins
- The TGA/PBD 2010 discussion paper on Similar Biological Medicinal Products
- Previous PBAC consideration of biosimilars
- The PBS and substitution at the pharmacist level ("a" flagging)
- Substitution of biosimilars in overseas jurisdictions.

TGA consideration of Basaglar

3.2 Basaglar (the trade name was previously Abasria®) was registered by the TGA on 21 November 2014 as:

> *"an insulin analogue indicated for once daily subcutaneous administration in the treatment of type 1 diabetes mellitus in adults and children and type 2 diabetes mellitus in adults who require insulin for the control of hyperglycaemia."*

3.3 Basaglar was submitted to the TGA as an abridged biosimilar submission.

3.4 The European Medicines Agency (EMA) has issued the following regulatory guidance for biosimilars in general, and for biosimilar insulin products:

- The Committee for Medicinal Products for Human Use (CHMP) of the EMA produced the first overarching biosimilar guideline, "Guideline on similar biological medicinal products." CHMP/437/04", in 2005;
- CHMP released an insulin-specific guideline in 2006 (EMEA/CHMP/BMWP/32775/2005); and
- The Biosimilar Medicinal Products Working Group (BMWG) produced a concept paper for revision of the guideline in 2011; and a revised guideline has been produced (EMEA/CHMP/BMWP/32775/2005_Rev.2).

3.5 In summary, the EMA regulatory guidelines for insulin biosimilars are more stringent than for new brands of non-biological medicines. The EMA guidelines for insulin biosimilars require the applicant to conduct a mix of pharmacodynamic, pharmacokinetic and clinical studies. In contrast a new brand of a small chemical molecule drug used in the treatment of diabetes, for example pioglitazone, would only be required to demonstrate bioequivalence.

3.6 The TGA Delegate's Overview noted that, for Basaglar "The sponsor's clinical development program was conducted according to EMA guidelines and after discussion with EMA" (page 1 of Delegate's Overview).

3.7 The Delegate's Overview goes on to say:

> "the draft CHMP guidance states that PK/PD insulin clamp studies represent the mainstay of the proof of similar efficacy of the biosimilar insulin and the reference product. The guidance further states that Phase-3 efficacy studies cannot be used to establish efficacy because the endpoints HbA1c are not sufficiently sensitive for the purposes of showing biosimilarity. In other words, Phase-3 studies (endpoint: HbA1c) only provide supportive evidence of efficacy; the pivotal evidence for claims of equivalent efficacy must come from the PK/PD studies. (The main role of the Phase-3 studies is to establish safety [and exclude any reduction in efficacy]; by measuring immunogenicity endpoints.)" (page 5-6 of Delegate's Overview)

3.8 The Advisory Committee on Prescription Medicines (ACPM) resolution stated that the ACPM:

> "considered that the data demonstrated that Abasria (Basaglar) and Lantus EU are equivalent in terms of pharmacokinetics and that Lantus USA and Lantus EU are also equivalent to each other in terms of pharmacokinetics." And that the "pharmacodynamics results are not statistically different for Lantus EU compared to Abasria (Basaglar)". (pg 3 of the ACPM Resolution).

[redacted]

PBS History of insulin glargine and other insulins

3.9 Insulin glargine (Lantus) was first recommended by the PBAC at its March 2006 extraordinary meeting on a cost effectiveness basis. The PBAC recommended the listing of insulin glargine on the basis that the clinical benefit over NPH insulin (improvement in hypoglycaemic event rates) in some patients was similar to the clinical benefit shown for insulin lispro over neutral insulin. In March 2006, the PBAC concluded that insulin glargine offers a small hypoglycaemia benefit over NPH, in some, but not all patients.

3.10 Basaglar was the first insulin glargine biosimilar registered in Australia and has not been previously considered by PBAC. No other insulin biosimilar had previously been registered by TGA or considered for PBS subsidy by PBAC.

2010 TGA/PBD Discussion Paper on Similar Biological Medicinal Products

3.11 In July 2010, the TGA and the Pharmaceutical Benefits Division (PBD) issued a joint discussion paper on Similar Biological Medicinal Products (SBMPs, also known as biosimilars). This paper captured policy that was current at the time the first biosimilars were considered by PBAC.

3.12 In the five years since this discussion paper was released, biosimilars policy has evolved such that the discussion paper is no longer current and has been removed from the PBS website.

Previous PBAC consideration of biosimilars

3.13 The PBAC has previously recommended the subsidy for biosimilars of epoetin alfa and filgrastim.

3.14 The epoetin alfa biosimilar is registered in Australia under the Australian Biological Name (ABN), epoetin lambda, trade name Novicrit (Sandoz). Filgrastim has three registered biosimilars, all with the same ABN as filgrastim. These products are marketed as Nivestim (Hospira), Zarzio (Sandoz) and TevaGrastim (Aspen).

3.15 The Novicrit epoetin lambda was recommended for subsidy by the PBAC in July 2010. At the time PBAC made this recommendation, there were already two epoetins on the PBS – epoetin alfa and epoetin beta. These had been declared to be different PBS drugs under section 85(2) of the Act. Epoetin lambda was subsequently also

declared a different drug, and all three epoetin drugs remain on the PBS F1 formulary.

3.16 The PBAC recommended the listing of filgrastim products as biosimilars of Neupogen®: Nivestim® (November 2010 meeting); TevaGrastim® (November 2011) and Zarzio® (March 2013). The PBAC recommended listing of the two latest products under the same listing conditions and price as Nivestim.

The PBS and substitution at the pharmacist level ("a" flagging)

3.17 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 of Pharmaceutical Benefits issued by the Department of Health states that the specified benefit and the substitute benefit are equivalent. The relevant section of the Act is reproduced below.

Extract from *National Health Act 1953*
s103 Offences
…

(2) Except as prescribed, a pharmacist to whom a prescription is presented shall not:
(a) supply, in purported pursuance of this Part, anything other than the pharmaceutical benefit that is directed to be supplied in the prescription; or
(b) in exchange for the prescription make a payment in money or give any other consideration to the person presenting the prescription.

Penalty: $2,000 or imprisonment for 12 months, or both.

(2A) Paragraph (2)(a) does not prohibit a pharmacist from supplying, instead of the pharmaceutical benefit that is directed to be supplied in a prescription (the specified benefit), another pharmaceutical benefit (the substitute benefit) if:
(a) the person who prescribed the specified benefit did not indicate on the prescription that only that benefit was to be supplied; and
(b) the Schedule of Pharmaceutical Benefits issued by the Department states that the specified benefit and the substitute benefit are equivalent; and
(c) the substitute benefit is a listed brand of a pharmaceutical item; and
(d) the supply of the substitute benefit is not prohibited by a law of the State or Territory in which the substitute benefit is supplied.

3.18 The Schedule of Pharmaceutical Benefits (Schedule) uses "a" flags to indicate that different pharmaceutical benefits are equivalent for the purposes of substitution by the pharmacist at the time of dispensing. An "a" flag can apply to different brands of the same pharmaceutical item or to different forms of different pharmaceutical items. Where substitution between different forms of pharmaceutical items is permitted, a note stating the specified forms are equivalent for the purposes of substitution is included.

3.19 The explanatory notes to the Schedule provide the following definition of brand equivalence:

Extract from the Explanatory Notes to the PBS Schedule

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.

For other brands of an item, i.e., those not indicated as above, it is unknown whether or not they are equivalent. There may be several reasons for this, such as bioequivalence data not being considered necessary when the products were approved for marketing, or that advice or data have not been forthcoming from sponsors. This does not necessarily suggest a lack of safety or efficacy, but in these circumstances caution should be taken if brands are interchanged.

'b' attached to brand names indicates that these brands are also equivalent, but that it is not known if there is equivalence between brands marked 'a' and brands marked 'b'.

Substitution of biosimilars in overseas jurisdictions

3.20 The approach taken by various overseas jurisdictions to the substitution of biosimilar brands of the same drug at the pharmacist level was examined by Tóthfalusi [2014]. In summary, Tóthfalusi found:

- In the EU, the procedures of approving a biosimilar and making a statement about its interchangeability are clearly separated. The first is a centralized procedure, i.e. the decision is made at the Community level. In contrast, the issue of substitutability is delegated to the national level. In the 28 member states, different usage patterns have emerged such as substitution in special cases, switching, or restricting the use of biosimilars only to previously untreated patients. The scientific background behind these policies is unclear but setting clear criteria for interchangeability and prescribability are not planned in any of the member states or at the EU level.
- The position of Health Canada on the substitution of biological products (biosimilars are called “subsequent-entry” products in Canada) is: “Health Canada does not support the automatic substitution of a subsequent-entry biologic for its reference biologic drug. Health Canada therefore recommends that physicians make only well-informed decisions regarding therapeutic interchange”. Funds for the reimbursement of pharmaceutical expenses are dispensed by the provinces.

3.21 More recent information provided to the Department indicated that some Canadian provinces are allowing substitution of biosimilars for treatment - naïve patients only.

3.22 Barlas 2014[1] reported that, in the US, the BCPI Act of 2009 'allows the FDA to declare a biosimilar interchangeable – and thereby substitutable without a physician's consent - if two conditions are met. The biosimilar must be expected to produce the same clinical result in any given patient, and the risk in terms of safety or diminished efficacy cannot be greater for a switch from a patented to a biosimilar product than continued use of the innovator drug, when the drug is used more than once by the same patient.' Barlas also outlines that it is up to individual states, under pharmacy practice statutes, whether pharmacists have to notify physicians when pharmacists substitute an interchangeable biosimilar for the innovator biologic.

3.23 [redacted]

4 Clinical place for the proposed therapy

4.1 The submission requested an identical place in the clinical management of type 1 and type 2 diabetes to Lantus. The submission claimed that no other changes in the clinical management of type 2 diabetes are expected as a result of using Basaglar in place of Lantus.

5 Comparator

5.1 The minor submission appropriately nominated Lantus as the comparator.

6 Clinical Trials

6.1 The clinical evidence presented in the submission was based on two phase 3 trials, which are outlined in the table below. The primary objective of both trials was to test the non-inferiority of Basaglar to Lantus as measured by change in HbA1c from baseline to 24 weeks.

Trials and associated reports in the submission

Trial ID	Brief Description and list of associated reports
ABEB (ELEMENT 1) NCT: 01421147	Description: Phase 3, randomized, multicenter, 2-arm, active-controlled, open-label, parallel, 24-week treatment study to compare LY2963016 [BASAGLAR] and LANTUS® with mealtime insulin lispro in adult patients with type 1 diabetes mellitus with a 28-week extension and a 4-week post-treatment follow-up.
	Main report: I4L-MC-ABEB Final Clinical Study Report (10th September 2013)
	Additional citations: None
ABEC (ELEMENT 2) NCT: 01421459	Description: Phase 3, randomized, multicenter, 2-arm, active-controlled, double-blind, parallel, 24-week treatment study (with a 4-week post-treatment follow-up) to compare LY2963016 [BASAGLAR] and LANTUS® in adult patients with type 2 diabetes mellitus.
	Main report: I4L-MC-ABEC Clinical Study Report (12th March 2013)
	Additional citations: None

Source: Section B, p22 of the submission

6.2 The TGA considered that these two Phase 3 studies (ABEB, ABEC) provided supportive evidence for efficacy and that the primary focus of the two studies 'was

[1] Barlas, S. "The Pharmaceutical Industry Tussles Over Biosimilars: Federal and State Decisions Will Have a Big Impact on Pharmacists." Pharmacy and Therapeutics 39.4 (2014): 278-80.

the evaluation of immunogenicity and implications this might have for safety (or any reduction in efficacy).' The pharmacokinetic and pharmacodynamic studies that the TGA relied on as pivotal evidence to demonstrate equivalent efficacy are discussed in paragraphs 6.9 to 6.12.

6.3 The key features of the ABEB study (also referred to as ELEMENT 1) and ABEC study (also referred to as ELEMENT 2) are presented in in the table below. Of particular note:

- ABEB was conducted in patients with type 1 diabetes, while ABEC was conducted in patients with type 2 diabetes.
- Patients in ABEB were on basal-bolus insulin for at least one year prior to enrolment, and patients in ABEC were on at least two oral anti-hyperglycaemic medicines with or without Lantus.

Prior insulin exposure

- With regard to prior exposure to insulin glargine, all patients in ABEB were on basal-bolus insulin for at least one year prior to enrolment, and 84.5% were on Lantus as their basal insulin. ABEC enrolled a mixture of patients who were insulin-naïve and patients who were on Lantus; In ABEC 39.6% of patients were on Lantus at enrolment.
  The table below outlines the trial protocols for switching from Lantus to the study drug. Patients who were on Lantus and switched to Basaglar seem to have directly switched at a dose equivalent to the dose of Lantus that was ceased, followed by titration.
- The pre-PBAC response outlined that, "in the ABEB (ELEMENT-1) and ABEC (ELEMENT-2) trials, the medical supervision for patients switching from Lantus to Basaglar was not different from the supervision in patients who stayed on Lantus. Both patient groups followed the same visits schedule to assess patients' response to study drug which included in-office visits and telephone visits. In both trials, patients who switched from Lantus to Basaglar demonstrated similar glycaemic control and safety profile (hypoglycaemia rate, AEs, immunogenicity) to patients who remained on Lantus."

Concomitant anti-hyperglycaemic therapy

- Patients in ABEB received pre-meal short acting insulin (insulin lispro) three times daily and Basalgar or Lantus once daily.
- Patients in ABEC continued their pre-study oral anti-hyperglycaemic medicines and received Basalgar or Lantus once daily.

Key features of the two phase 3 trials presents (ABEB and ABEC)

	ABEB (ELEMENT 1)	ABEC (ELEMENT 2)
Patient population	Type 1 diabetes On basal-bolus insulin for at least one year.	Type 2 diabetes on at least two oral anti-hyperglycaemic medicines (+/- Lantus).
Number of participants	534	756
Study design	Non-inferiority (pre-defined margin of 0.4% and 0.3% change in HbA1c)	Non-inferiority (pre-defined margin of 0.4% and 0.3% change in HbA1c)
Primary outcome	change in HbA1c from baseline to 24 weeks	change in HbA1c from baseline to 24 weeks
Concomitant medicines	In combination with pre-meal insulin lispro (short acting insulin, three times a day)	in combination with other oral anti-diabetes medicines
Previous insulin therapy	Had to be on basal-bolus insulin for at least 1 year (page 56 of CSR)	Patients were either: - insulin naïve with inadequate glycaemic control, or - on LANTUS with adequate or inadequate glycaemic control
Percent of patients on basal insulin at study commencement	100% - 84.5% on Lantus - 15.5% on 'other'	39.6% on Lantus 60.4% on none (per page 86 of CSR)
Study blinding	Open label for subjects and investigators (but assessors were blinded)	Double-blinded
Duration of treatment	24 weeks	24 weeks
Duration of follow-up	32 weeks (56 weeks from commencement)	4 weeks (28 weeks from commencement)
Dosage regimen during the trial (Study protocol for switching from Lantus onto study drug)	Basaglar: The dose of Basaglar was equivalent to the dose of the individual patient's pre-study QD basal insulin that was discontinued. Basaglar was administered subcutaneously QD. Lantus The dose of Lantus was equivalent to the dose of the individual patient's pre-study QD basal insulin that was discontinued. Lantus was administered subcutaneously QD.	Basaglar: Insulin naive: Starting dose 10 IU QD, followed by patient-driven titration of 1 IU/day until FBG ≤100 mg/dL (5.6 mmol/L). Patients entering from Lantus: Starting dose equivalent to Lantus, followed by patient-driven titration of 1 IU/day until FBG ≤100 mg/dL (5.6 mmol/L). Basaglar was administered subcutaneously QD. Lantus Insulin naïve with inadequate glycaemic control: Starting dose 10 IU QD, followed by patient-driven titration of 1 IU/day until FBG ≤100 mg/dL (5.6 mmol/L). Patients entering on Lantus (with adequate or inadequate glycaemic control) started on an equivalent dose. Lantus was administered subcutaneously QD.

Source: Complied during evaluation.
Abbreviations: QD = once daily: IU = international unit; FBG = fasting blood glucose; QD = once daily

Patient population enrolled in the phase 3 trials

6.4 The table below summarises the baseline characteristics of patients recruited in the phase 3 trials.

Baseline disease characteristics in ABEB and ABEC

	ABEB/ELEMENT 1 (T1DM)			ABEC/ELEMENT 2 (T2DM)			
	Basaglar (N= 268)	Lantus (N=267)	Overall (N=535)	Basaglar (N= 376)		Lantus (N=380)	Overall (N=756)
Duration of diabetes (years)							
Mean (SD)	16.23 (11.0)	16.56 (10.83)	16.39 (10.91)	11.66 (6.79)		11.24 (6.82)	11.45 (6.80)
Range	1.00, 54.31	1.13, 55.20	1.00, 55.20	0.52, 40.44		0.44, 33.45	0.44, 40.44
Baseline HbA1c (%)							
Mean (SD)	7.75 (1.13)	7.79 (1.03)	7.77 (1.08)	8.34 (1.09)		8.31 (1.06)	8.33 (1.08)
Range	4.80, 11.50	5.20, 10.30	4.80, 11.50	4.90, 11.30		5.90, 11.20	4.90, 11.30
Entry basal insulin, n (%)							
Lantus	218 (81.3)	234 (87.6)	452 (84.5)	155 (41.2)		144 (37.9)	299 (39.6)
Other	50 (18.7)	33 (12.4)	83 (15.5)	221 (58.8)		236 (62.1)	457 (60.4)
Entry short-acting insulin, n (%)				Sulfonylurea use, n (%)			
Insulin lispro	124 (46.4)	121 (45.3)	245 (45.9)	Yes	315 (83.8)	315 (82.9)	630 (83.3)
Other	143 (53.6)	146 (54.7)	289 (54.1)	No	61 (16.2)	65 (17.1)	126 (16.7)
Body weight (kg)							
Mean (SD)	75.80 (16.76)	74.77 (15.36)	75.29 (16.07)	90.35 (20.02)		89.83 (19.25)	90.09 (19.62)
Range	42.40, 117.70	43.40, 120.00	42.40, 120.00	49.50, 165.40		44.20, 176.00	44.20, 176.00

Source: Section B of the submission (p27) [a]*Page 86 of CSR clarifies that this row is 'None', not 'Other' as reported in the submission*.

Comparative effectiveness

Non-inferiority to Lantus®

6.5 Both studies nominated a pre-specified non-inferiority margin of 0.4% change in HbA1c. If the 0.4% non-inferiority margin was met, the upper limit of the 95% CI was compared with the 0.3% non-inferiority margin. This is reasonable and in line with PBAC's previous acceptance of a minimum clinical important difference (MCID) of 0.3% - 0.4% for anti-hyperglycaemic agents.

6.6 The trial results for the primary outcome from the Phase 3 studies are summarised in the table below.

Change in HbA1c (%) from ABEB and ABEC (24 weeks)

	ABEB (T1DM) n=535		ABEC (T2DM) n=756	
Full analysis set				
HbA1c (%)	Basalgar n=267	Lantus n=267	Basalgar n=369	Lantus n=375
Least squares mean change from baseline (LOCF)	-0.352 (0.053)	-0.460 (0.054)	-1.286 (0.06)	-1.338 (0.06)
LS mean difference (95% CI)	0.108 (-0.002, 0.219)		0.052 (-0.070, 0.175)	
Per protocol analysis set				
HbA1c (%)	Basaglar n=251	Lantus n=256	Basalgar n=314	Lantus n=308
Least squares mean change from baseline (LOCF)	-0.370	-0.468	-1.286	-1.338
LS Mean difference	0.098 (-0.014, 0.209)		0.116 (-0.010, 0.242)	

Source: Tables B7 and B9 of the submission, Delegate's Overview
Abbreviation: LOCF- last observation carried forward

6.7 The LS mean difference between treatments (Basaglar – Lantus) in change from baseline to the 24-week endpoint (LOCF) was 0.108% (95% CI: -0.002%, 0.219%) for the ABEB study and 0.052% (95% CI: -0.070%, 0.175%) for the ABEC study. As the upper limit of the 95% CI for the LS mean difference is <0.3%, non-inferiority of Basaglar to Lantus was demonstrated at both the 0.4% and 0.3% non-inferiority margins, in both studies.

6.8 The TGA Delegate's Overview (pg10) stated that the results from ABEB and ABEC 'meet the non-inferiority margin 0.3% at 24 weeks for the endpoint of "change in HbA1c", although the point estimates show that Basaglar was slightly worse than Lantus, in terms of HbA1c.'

Pharmacokinetic/Pharmacodynamic studies

6.9 Six pharmacokinetic/pharmacodynamic studies were presented to the TGA in support of the claim of biosimilarity. The ABEA insulin clamp study in healthy volunteers was the pivotal study that the TGA used to establish biosimilarity, and the details of this study are summarised in the table below.

Pivotal study details used to determine efficacy by the TGA

Study	Objective	Design	Treatments	Healthy Subjects N
ABEA	Comparison of the PK and PD of Basaglar and EU Lantus	Phase 1, single-center, randomized, subject and investigator blind, 4 period replicate crossover, 24 hour euglycaemic glucose clamp study	Single 0.5-U/kg doses of Basaglar and Lantus administered by SC injection	N=80 (56 males/ 24 females) Mean age – 32 years (18-60) Mean BMI = 24.9 (19.4-32.0)

Source: Clinical Evaluation Report (p83)
Abbreviations: PK- pharmacokinetics, PD- pharmacodynamics, EU-European Union, SC- subcutaneous, N- number of subjects enrolled, BMI- body mass index

6.10 The results of ABEA are summarised in the table below.

Results for pivotal ABEA study in healthy volunteers, with insulin dose of = 0.5 U/kg

Pharmacokinetic (PK) parameters		Pharamcodynamic (PD) parameters	
AUC[0-24] pmol.hr/L n Point estimate (90% CI)	Cmax pmol/L n Point estimate (90% CI)	Gtot mg/Kg n Point estimate [95% CI]	Rmax mg/Kg n Point estimate [95% CI]
N = 76 0.91 (0.87, 0.96)	n=78 0.95 (0.91, 1.00)	n=78 0.95 [0.90, 1.01]	n=78 0.99 [0.93, 1.05]

Source: TGA Delegate's Overview (p6)
Abbreviations: Gtot (total amount of glucose infused during the euglycaemic clamp procedure)
Rmax (maximum glucose infusion rate)

6.11 The Clinical Evaluation Report stated that "The AUC and Cmax were indicative of biosimilarity using the 90% confidence intervals of 80%-125% acceptance limits. The comparative PK and PD studies demonstrated highly similar PK and PD of Basaglar to Lantus (ABEA) within predefined bioequivalence acceptance limits" (p 14).

6.12 The ACPM 'advised that acceptable similarity between Abasria (Basaglar) and Lantus had been demonstrated by the PK and PD studies' (page 2 of ACPM Ratified minutes).

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

Comparative harms

6.13 The table below summarises the adverse events reported in the ABEB and ABEC trials.

Summary of adverse events reported in ABEB and ABEC trials

	ABEB			ABEC		
	52 weeks			24 weeks		
	Basaglar n (%)	Lantus n (%)	p-value	Basaglar n (%)	Lantus n (%)	p-value
Deaths	1 (0.3)	1 (0.3)	>0.999	0 (0.0)	1 (0.4)	
Serious Adverse Events	15 (4.0)	18 (4.7)	0.723	20 (7.5)	24 (9.0)	0.534
Discontinuations due to Adverse Events	6 (1.6)	11 (2.9)	0.327	2 (0.7)	6 (2.2)	0.176
Injection site Adverse Events	13 (3.5)	11 (2.9)	0.684	7 (2.6)	3 (1.1)	0.339
Treatment-Emergent Adverse Events	196 (52.1)	184 (48.4)	0.310	167 (62.3)	166 (62.2)	>0.999
TEAE possibly related to study drug	26 (6.9)	23 (6.1)	0.660	17 (6.3)	14 (5.2)	0.712
TEAE possibly related to study procedure	6 (1.6)	8 (2.1)	0.789	2 (0.7)	2 (0.7)	>0.999
TEAE possibly related to study disease state (diabetes)	19 (5.1)	18 (4.7)	0.868	21 (7.8)	16 (6.0)	0.496
TEAE with special topic assessment of adverse (allergic) events	21 (5.6)	27 (7.1)	0.456	20 (7.5)	11 (4.1)	0.138

Source: Table B-11 and B-14 of the submission

Abbreviations: AEs = adverse events; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events

6.14 The Delegate's Overview (pages 9-10) stated that "there were no imbalances in serious adverse events or deaths", and ''there were no clinically meaningful differences in total, severe or nocturnal hypoglycaemia for Basaglar versus Lantus", and "there were no differences in treatment-emergent allergic events (e.g arthralgia, pruritus, rash, asthma, injection-site reactions). The majority of these events were mild and none led to discontinuation."

<u>Immunogenicity/Proportion of patients with detectable insulin antibodies</u>

6.15 The Delegate's Overview outlined the history of, and rationale for, immunogenicity concerns with biosimilars (pages 2-3).

6.16 The Delegate's Overview stated:

> "The general corresponding concern for biosimilars is that even small and innocuous differences in manufacture, formulation, or presentation could lead to unforseen clinical consequences associated with immunogenicity, which could lead to reduced efficacy or new safety problems." (pg 3)

6.17 The Delegate's Overview (pg 3) stated that 'formation of antibodies to insulin occurs frequently, without major consequences for efficacy and safety'. The Overview further stated 'Antibodies could have an effect on efficacy, with larger doses of insulin

required (neutralising antibodies) or safety, with injection site reactions or very rarely IgE mediated anaphylaxis (non-neutralising antibodies).'

6.18 The TGA evaluated the proportions of patients with detectable antibodies and treatment-emergent antibody response in the two phase 3 studies. "The ACPM advised that the results from the two phase III clinical trials (ABEC and ABEB) demonstrated similarity of the two products, including for immunogenicity." (page 2 of the ACPM Resolution). The results are outlined in in the table below.

Proportion of patients with detectable insulin antibodies at baseline, endpoint, and overall (anytime), ABEB, ABEC, to 24 weeks

	ABEB (T1DM) N=535		ABEC (T2DM) N=756	
	Basaglar N=265 n (%)	Lantus N=267 n (%)	Basaglar N=365 n (%)	Lantus N=365 n (%)
Baseline	45 (17)	55 (21)	20 (6)	13 (4)
Endpoint (LOCF)	50 (19)	51 (19)	30 (8)	22 (6)
Overall (anytime)	79 (30)	90 (34)	56 (15)	40 (11)

Source: Delegate's Overview, page 8. a) overall (anytime) during treatment period, not including baseline

6.19 The Clinical Study Report for ABEC (ELEMENT-2) presented a subgroup analysis for the incidence of Treatment Emergent Antibody Response by entry basal insulin treatment (that is, whether patients were taking Lantus® or no insulin at baseline).

The Delegate's Overview stated:

> "For ABEC, a difference in the proportion of patients with detectable antibodies was reported for insulin-naïve patients (e.g., overall [anytime] at 24 weeks: Abasria (Basaglar) 19% versus Lantus 8%). This is difficult to interpret, given the multiple statistical comparisons. Also, no difference was found in study ABEB, which was the study with the most sensitive population for detecting immunogenicity (i.e., T1D)."

The Delegate's Overview (pg 9) stated that "for ABEB, at 52 weeks, the proportions of patients with detectable antibodies was similar." Note that all patients in ABEB were on basal insulin prior to enrolment, and 84.5% were on Lantus.

Pharmacovigilance

6.20 "The EMA guidelines suggest the implementation of a pharmacovigilance programme that will rapidly detect any clinically significant immunogenicity that may emerge over extended time periods" (page 4 of the Delegate's Overview).

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

Clinical claim

6.21 The submission claimed non-inferior comparative effectiveness and non-inferior comparative safety of Basaglar compared to Lantus.

6.22 The PBAC noted that the ACPM was satisfied that the submitted data (including ABEB and ABEC) showed that Basaglar is similar to Lantus in terms of efficacy and safety and the TGA registered Basaglar as a biosimilar medicine. Therefore, the clinical claim appears to be reasonable.

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

Other matters – "a" flagging

6.23 As outlined in Paragraphs 1.1 and 1.2, the Minister (delegate) requested PBAC provide advice, under sub-section 101(3) of the Act, on the marking of Basaglar and Lantus as equivalent for the purposes of substitution by the pharmacist at the point of dispensing (i.e., "a" flagged in the Schedule of Pharmaceutical Benefits).

[redacted]

6.24 [redacted]

[redacted]

[redacted]

[redacted]

Economic analysis

6.25 The submission presented a cost minimisation analysis against Lantus. Based on the results of the two phase 3 trials (ABEB and ABEC), the submission proposed that

100IU/ml of Lantus is equivalent to 100IU/ml of Basaglar. This is consistent with PBAC guidelines and TGA's acceptance of biosimilarity between Basaglar and Lantus.

6.26 The submission factored in the impact of the 16% statutory price reduction that it stated "is expected to apply to all brands of insulin glargine" (pg 43)." This is consistent with the statutory price reduction provisions of the Act. The listing of Basaglar on the PBS would also result in insulin glargine being moved to the F2 formulary and being subject to price disclosure.

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

Estimated PBS usage & financial implications

6.27 The current market growth for Lantus was extrapolated using PBS item report data from November 2009 to October 2014. [redacted]

[redacted]

Estimated market share of Basaglar as a total of the insulin glargine market

	Year 1	Year 2	Year 3	Year 4	Year 5
Basaglar market share	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Source: Section E of the submission

6.28 The minor submission estimated a net save to the PBS of $[redacted] million over five years of listing. The submission assumed that replacement of Lantus with Basaglar will be on a 1:1 basis. [redacted]

6.29 The financial implications are summarised in the table below.

Estimated overall net cost of listing Basaglar to the PBS and RPBS over five years

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated number of Basaglar scripts dispensed					
PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated overall net cost of listing Basaglar on the PBS (savings are largely due to the 16% statutory price reduction to all insulin glargine products)					
Overall net cost to the PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall net cost to the RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall net cost to the PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combined overall net cost to the PBS/RPBS over five years	[redacted]				

Source: Section E of the submission

The redacted table above shows:
Estimated financial impact: Savings of $20 - $30 million per year in Year 1, increasing to savings of $30 -$60 million per year in Year 5.

6.30 The costs were estimated using a DPMQ of $[redacted] per script of Basaglar (5 packs containing 5 x 3mL cartridges/pens), which included the 16% price reduction that would be triggered upon listing Basaglar.

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

7 PBAC Outcome

7.1 The PBAC recommended the unrestricted benefit listing of the biosimilar insulin glargine Basaglar® for the treatment of type 1 and 2 diabetes mellitus on a cost-minimisation basis with insulin glargine Lantus. The equi-effective doses are 100 IU/mL Basaglar and 100 IU/mL Lantus.

7.2 The PBAC considered that the claim of non-inferior comparative effectiveness and non-inferior comparative safety was adequately supported. The PBAC noted that the ACPM was satisfied that the submitted data (including from the clinical trials ABEB and ABEC) showed that Basaglar is similar to Lantus in terms of efficacy and safety, and further noted that the TGA registered Basaglar as a biosimilar medicine.

7.3 [redacted]

[redacted]

7.4 In a broader context, the PBAC foreshadowed that it is of a mind to consider whether a biosimilar medicine is suitable for substitution by pharmacists on the basis of each application on its own merit, based on the evidence presented in each case, rather than adopting an overall policy-position *a priori*.

7.5 The PBAC noted the submission estimated net overall savings to the PBS/RPBS of approximately $[redacted] over the first five years of listing. This was based on the impact of the statutory 16% price reduction following the listing of a biosimilar brand. The financial estimates did not account for any potential impacts of price disclosure.

7.6 The PBAC advised that Basaglar is suitable for prescribing by nurse practitioners, as with Lantus.

7.7 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
INSULIN GLARGINE Insulin glargine 100 international units/mL injection, 5 x 3 mL cartridges	5	1	[redacted]

*Trade name was previously Abasria®

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☒Medical Practitioners ☒Nurse practitioners
Restriction Level / Method:	Unrestricted

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

The Sponsor had no comment.