7.10 INSULIN GLARGINE 3 ml cartridges, 100 IU/ml, Basaglar®, Eli Lilly

1 Purpose of submission

1.1 The minor submission requested further advice from the PBAC regarding its previous recommendation (March 2015) for the PBS listing of the biosimilar insulin glargine, Basaglar®.

2 Background

2.1 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."*

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

2.3 The PBAC previously considered Basaglar at the March 2015 PBAC meeting.

2.4 At this time, 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.

2.5 The PBAC further advised the Minister that it considered the Basaglar and Lantus brands of insulin glargine cartridges could be marked as equivalent in the Schedule for the purposes of substitution by the pharmacist at the point of dispensing. Further, the PBAC advised that Basaglar KwikPen and Lantus Solostar brands of insulin glargine pre-filled disposable pens could also be marked as equivalent in the Schedule for the purposes of substitution. However, the PBAC considered that the differences between the cartridges (for use in re-usable pens) versus pre-filled disposable pens were sufficient to preclude substitution between cartridges and pre-filled disposable pens.

2.6 In forming its view on brand substitution ("a" flagging), the PBAC considered a range of factors including that patient response is monitored regularly (through self-monitoring or diabetes educators), and that dose titration occurs routinely in current practice as insulin dose requirements may vary frequently, for example due to intercurrent illness or changes in diet. The PBAC further noted that approximately 81% and 41% of patients switched from Lantus to Basaglar in the Basaglar arm of the ABEB and ABEC trials respectively, albeit the patients switched brands once only.

2.7 The PBAC noted that:

- The current TGA Product Information for Basaglar states that the "replacement of Lantus with Basaglar, or vice versa, should take place only under the supervision of the prescribing medical practitioner", and this statement is in line with the TGA guidance paper "Evaluation of Biosimilars", V1.0, July 2013, pg 17 [http://www.tga.gov.au/pdf/pm-argpm-biosimilars.pdf]. It is also consistent with the 2010 TGA/PBD discussion paper on Similar Biological Medicinal Products, which is no longer current.
- Basaglar and Lantus are both cartridges for use with a compatible re-usable pen. Basaglar KwikPen and Lantus Solostar are both pre-filled disposable pens. The PBAC noted that substituting between a cartridge for use in a re-usable pen and a disposable pen may require specific training particularly around loading cartridges into a pen device.

2.8 The PBAC also noted that the ACPM has 'advised that acceptable similarity between Abasria (Basaglar) and Lantus has been demonstrated by the PK and PD studies' (ACPM Resolution, October 2014). Given also that patients with diabetes currently experience variability in their response to the same brand of insulin, have their response to insulin monitored very closely and have their doses titrated accordingly, the PBAC advised that it would expect that these brands may be interchanged (substituted) without differences in clinical effect beyond the variability in response seen within any one brand of insulin (i.e. the PBAC considered that the risk in terms of safety and diminished efficacy is not necessarily greater for a switch between Basaglar and Lantus, than for continued use of Lantus or Basaglar).

2.9 The PBAC also considered that any differences in the re-usable pen devices, can be managed in the course of the regular patient education and counselling on the use of the devices that is provided to patients by prescribers, pharmacists and diabetes educators, and that these differences were not sufficient to preclude marking the two brands as equivalent. Similarly, the PBAC considered that any differences in the pre-filled disposable pen devices can be managed in the course of the regular patient education and counselling.

3 Consideration of the evidence

Sponsor hearing

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

Consumer comments

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

3.3 The introduction to the resubmission stated:

"The purpose of this submission is to request further advice from the PBAC regarding its previous recommendation for the PBS listing of Basaglar.

The focus of this submission is to respond to various aspects associated with substitution of Basaglar and Lantus by the pharmacist at the point of dispensing. It will focus on three points:

1. The evidence base required to enable substitution at the pharmacy level
2. Potential safety implications associated with substituting Basaglar and Lantus in clinical practice.
3. Inconsistencies between the PBAC recommendation and TGA determination."

3.4 The key issue being considered in the resubmission and this overview is the substitutability of Basaglar and Lantus, as the efficacy and safety of Basaglar has previously been assessed and accepted by the PBAC. However, some additional safety related data related to immunogenicity and antibodies, as well as a summary of a review regarding switching biologicals has also been included.

Insulin glargine safety

3.5 Regarding the impact of insulin antibodies, the March 2015 PBAC Minutes (paragraph 6.17) include the following quotes from the Basaglar Delegate's Overview:

'formation of antibodies to insulin occurs frequently, without major consequences for efficacy and safety'; and

'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).'

3.6 Similarly the Australian Product Information (PI) for Lantus[1] states:

'In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyperglycaemia or hypoglycaemia.'

3.7 The Canadian Product Monograph for Lantus[2] notes that a review of the clinical data has not identified a need for dose adjustments due to insulin antibodies. Specifically, the following statement is included in the PI:

"Insulin administration may cause insulin antibodies to form. In clinical studies, antibodies that cross-react with human insulin and insulin glargine were observed in both NPH human insulin and insulin glargine treatment groups with similar percents of increased and decreased titers. There was no correlation in either treatment group between increases or decreases in these antibody titers and changes in either A1C or total insulin requirements. In theory, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyperglycaemia or hypoglycaemia, but has not been found on review of LANTUS clinical trials and available post-marketing data."

[1] p.19, Australian PI for Lantus®, Insulin glargine, Sanofi, Date of most recent amendment 25 March 2014

[2] p.7. Canadian Product Monograph for Lantus®, Insulin glargine (rDNA origin), solution for injection 100 U/mL. Sanofi-aventis Canada Inc., version s-a 13.0 dated January 7, 2015

3.8 The proportion of patients with detectable insulin antibodies at baseline, study endpoint and overall was similar with Basaglar and Lantus in the ABEB and ABEC trials (March 2015 PBAC minutes, paragraph 6.18). The European Medicines Agency (EMA) further commented that "there was no evidence that these antibodies had any impact on efficacy and safety outcomes (HbA1c, weight, insulin dose, hypoglycaemic episodes, allergic or injection site reactions).."[3]. Data from the ABEB and ABEC trials published as a conference abstract[4] and poster[5] show that the incidences of treatment emergent antibody responses (TEAR) and treatment emergent allergic events did not differ (p>0.05) between Basaglar and Lantus (antibody responses: 10.9% vs 9.4% in ABEB, 3.8% vs 3.8% in ABEC; allergic events: 7.5% vs 4.1% in ABEB, 5.6% vs 7.1% in ABEC). It is also stated that clinical outcomes (HbA1c, basal insulin dose, and total hypoglycaemia) were not affected by TEAR status in ABEB or ABEC (p>0.05 for treatment-by-TEAR interaction for these outcomes).

General biosimilar safety

3.9 A review of data related to switching between therapeutic proteins was published in 2012[6]. The review included:

- 13 cross-over trials in 415 volunteers and growth-hormone deficient patients assessing growth hormone products;
- 35 cross-over trials in 11,249 volunteers and patients assessing erythropoietin products; and
- 10 trials in 374 volunteers and patients assessing granulocyte colony stimulating agents.

3.10 The review also included data from pharmacovigilance databases and literature on the frequency of switching between human recombinant growth hormones, erythropoietins and granulocyte colony stimulating agents. The authors concluded:

> "We were not able to identify direct safety risk associated with substituting biopharmaceuticals in any of the data sources we analyzed. Although there may be valid reasons to be prudent with switching between biopharmaceuticals, including traceability of adverse events or concerns about patient anxiety, thus far there is no evidence that the process of switching in itself poses a risk to patients. Currently, there is limited clinical data that specifically studied the effects of switching, but they mostly concluded that patients can be safely switched from one product to the other.
>
> However, most clinical trials included in our analysis were not designed to identify switching related adverse events, while spontaneous reporting systems may not be

[3] Pg. 58, European Medicines Agency, Assessment Report, Abasria, insulin glargine. Procedure No. EMEA/H/C/002835/0000

[4] Deeg, M, Ilag, L, et al. Evaluation of Immunogenicity of LY2963016 Insulin Glargine Compared with Lantus® Insulin Glargine in Patients with T1D or T2D. Abstract 70-OR. Presented at 74th American Diabetes Association (ADA) Scientific Sessions; June 13-17, 2014; San Francisco, CA, abstract presented in 141, Canadian Journal of Diabetes, 38 (2014) S51-S52

[5] http://www.easdvirtualmeeting.org/resources/18907, accessed 9 June 2015

[6] Ebbers HC, Muenzberg M, Schellekens H. The safety of switching between therapeutic proteins. Expert Opin Biol Ther. 2012 Nov;12(11):1473-85.

well equipped to identify adverse events associated with switching between biopharmaceuticals."

"Thus far there have been no safety concerns with marketed biosimilars. Although adverse events related to immunogenicity are a concern for most biopharmaceuticals including biosimilars and different products may be more or less immunogenic, there is no data that supports the notion that switching between different products induces immunogenicity."

3.11 Ebbers and Chamberlain 2014[7] state that no post-authorisation immunogenicity-related issues have yet been detected in the post-authorisation phase for any EU-approved bio similar product. Since April 2006, 19 biosimilars have been approved by the EMA. The medicines approved include insulin glargine, epoetin (alfa and zeta), filgrastim, follitropin alfa, infliximab and somatropin.

3.12 The PBAC noted the sponsor's responses in the pre-PBAC response.

Evidence for substitution at the pharmacy level

3.13 The resubmission presented three issues as being relevant to consideration of substitution at the pharmacy level:

- The evidence supporting substitution at the pharmacy level,
- The impact of substitution on the collection of longer term evidence of safety, and
- The substitutability of the devices used to deliver brands of insulin glargine.

<u>The evidence supporting substitution at the pharmacy level</u>

3.14 The minor resubmission noted (p2) that under the US Biologics Price Competition and Innovation (BCPI) Act of 2009 the FDA may declare a biosimilar as interchangeable and thereby substitutable without the physician consent, however, this requires additional data beyond those required to meet the biosimilarity standard. The submission states the required additional evidence does not exist within the Basaglar data package.

3.15 For the FDA to consider a product to be interchangeable, in addition to demonstrating biosimilarity, information must be provided to show that the proposed interchangeable product is expected to produce the same clinical result as the reference product in any given patient. In addition, for a biological product that is administered more than once to an individual, it must be demonstrated that the risk in terms of safety or diminished efficacy of alternating or switching between use of the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without such alternating or switching (resubmission p3).

[7] Ebbers HC and Chamberlain P. Interchangeability. An insurmountable fifth hurdle? GaBI Journal 2014; 3(2):88-93

3.16 The resubmission stated (p4) a clinical trial design that would provide the evidence that would satisfy the requirements of the FDA for interchangeability would involve switching and alternating between the biosimilar and reference products within an individual patient and would show that this practice adds no risk to patient safety. A cross-over design study with the following comparisons is noted to address both switching and alternating:

- biosimilar to biosimilar (BB);
- reference product to reference product (RR);
- biosimilar to reference product to biosimilar (BRB); and
- reference product to biosimilar to reference product (RBR).

3.17 The FDA has not yet published guidance on the information required to demonstrate a product is interchangeable[8]. The trial design discussed in the resubmission to assess interchangeability is that recommended by individual statisticians from two American and two Taiwanese Universities (Chow et al[9]). Ebbers et al 2014[10] have similarly suggested assessing multiple switches and consider that this could be incorporated into the required registration study(s). A number of designs are proposed. The simplest is a comparison of B, R and BRB. For infliximab the Norwegian Department of Health are funding a double-blind randomised trial comparing the safety and efficacy of switching from innovator infliximab (Remicade) to biosimilar infliximab compared with continued treatment with innovator infliximab (NOR-SWITCH study[11]). For inclusion patients must have been on stable treatment with innovator infliximab for at least 6 months. The planned sample size is 500 patients. The trial is due to be completed in April 2016. This trial is not assessing multiple switches between the innovator and biosimilar.

3.18 To date, the only biosimilar product approved using the pathway defined by the BCPI Act is Zarxio (filgrastim)[12]. This product has been approved as biosimilar. This product has not been assessed for interchangeability.

3.19 Basaglar received tentative FDA approval in August 2014[13]. All regulatory requirements were met; however, the approval is tentative because of litigation filed by Sanofi claiming patent infringement. Basaglar was approved under the 505(b) (2) pathway. Similar to the BCPI pathway, the 505(b) (2) pathway uses safety and effectiveness data of a previously approved product. The 505(b)(2) pathway is largely used to obtain approval of small-molecule drugs (eg. for approval of different dosage

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8 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf, accessed 3 June 2015

9 Chow et al Statistical methods for assessing interchangeability of biosimilars. Statist. Med 2013; 32: 442-448

10 Ebbers HC and Chamberlain P. Interchangeability. An insurmountable fifth hurdle? GaBI Journal 2014; 3(2):88-93

11 https://clinicaltrials.gov/ct2/show/study/NCT02148640

12 http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm, accessed 1 June 2015

13 http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/205692Orig1s000TAltr.pdf, accessed 10 June 2015

forms, formulations, combination products) but has also been used to obtain approval of products considered in Europe to be biosimilars (eg. somatropin, glucagon).

3.20 The 505(b) (2) pathway is only available for biologics that had been approved under a new drug application (NDA) before the BPCI Act was signed into law in March 23, 2010, and it is only available for these biologics until March 23, 2020. After this, biological products will be considered under the BPCI pathway.

3.21 As Basaglar was not considered under the BCPI pathway it was not assessed for interchangeability. The PBAC noted the sponsor's assertion in the pre-PBAC response that the 505(b)(2) pathway is analogous to the FDA biosimilar pathway in all scientific aspects and the FDA has the opportunity to issue an interchangeability determination for Basaglar through the 505(b)(2) pathway, by designation of an 'A' rating but so far has given no indication that it will do so.

3.22 The resubmission considered (p5) the data from the ABEB and ABEC trials would not be adequate for the assessment of switching as this would require switching and alternating between Lantus and Basaglar, in a clinical trial setting.

3.23 The submission's assertions regarding clinical trial designs are speculative as the FDA requirements for assessing interchangeability are yet to be defined, and as FDA did not consider, nor was it asked to consider the interchangeability of Basaglar and Lantus.

3.24 At the March 2015 meeting, the PBAC noted that approximately 81% of 268 patients and 41% of 376 patients switched from Lantus to Basaglar in the Basaglar arm of the ABEB (in type 1 diabetes patients) and ABEC (in type 2 diabetes patients) trials respectively, albeit the patients switched brands once only (paragraph 7.4 of March 2015 minutes). The resubmission notes (p4-5):

- the switch occurred at randomisation under direct medical supervision;
- no data are available from the period before the switch other than patients basal characteristics assessed at a single time point; and
- patients that received Lantus prior to randomisation did not receive it in a controlled clinical trial environment and hence, data regarding safety, dosage and compliance are incomplete.

3.25 Additional information regarding the design of the ABEB and ABEC trials is provided below.

ABEB Trial

3.26 In the ABEB trial, the insulin glargine (Lantus and Basaglar) was self-administered using pre-filled pens. Both bolus and basal insulins were switched in patients. At randomisation, all patients were switched from their pre-study bolus mealtime insulin (human regular insulin, or insulin analog lispro, aspart, or glulisine) to insulin lispro (ABEB CSR, p58 and p62). All patients were switched from their pre-study QD basal insulin (NPH, LANTUS®, or detemir) to either Basaglar or Lantus based on their random allocation (ABEB CSR, p58 and p62).

3.27 Titration of the basal or bolus insulin dose was investigator driven during phone and office visits. Most of the basal and bolus insulin dose adjustments occurred during the initial titration period (Weeks 0 through 6). However, titration was extended up to Week 12 for patients who needed more intensification to achieve glycaemic targets. Insulin dose adjustments during the maintenance period were for safety concerns such as hypoglycaemia or unacceptable hyperglycaemia. Patients who based their bolus insulin doses on carbohydrate-counting continued adjusting their doses accordingly to attain/maintain glycaemic goals (p62). Therefore, it is likely that patients continue to titrate their insulin lispro throughout the study period, on top of any adjustments for the insulin glargine.

3.28 Data are not recorded in the CSR for the period prior to the switch however, for inclusion in the ABEB trial, patients must have been on basal-bolus insulin therapy for at least 1 year prior to screening. Basal insulin was required to be QD injection of NPH, LANTUS®, or detemir for at least 3 months prior to screening and combined with mealtime injections of bolus insulin (ABEB CSR, p58). Patients had no more than one episode of severe hypoglycaemia, diabetic ketoacidosis or emergency room visit for uncontrolled diabetes leading to hospitalisation within the previous 6 months. Thus the trial included type 1 diabetes patients with stable disease.

3.29 This trial had a longer study period compared to ABEC. ABEB included a 24-week treatment period, a 28-week active-controlled extension period, and a 4-week post-treatment follow-up. Patients visited the investigator site at weeks 0, 2, 6, 12, 18, 24, 30, 36, 44, and 52 for study assessments (ABEB CSR, p56). Between visits 2 (week 0) and 3 (week 2), and visits 3 (week 2) and 4 (week 6), patients were contacted over the telephone to assess their response to the study drug and to further adjust insulin doses, if needed.

3.30 At baseline the LS mean HbA1c (%) was 7.76 and 7.79 in the Basaglar and Lantus group, respectively, and by 24 weeks this had reduced slightly to 7.42 and 7.33 (ABEB CSR, Table ABEB 11.2). The insulin glargine dose (either as Lantus or Basaglar) was increased by a mean of 2 units/day, between baseline and week 24 (ABEB CSR, Table ABEB.11.8). The insulin lispro dose reduced by a mean of 1 unit/day between baseline and week 24 (ABEB CSR, Table ABEB 11.9). Thus during the ABEB trial the patient's insulin glargine and bolus insulin dose was reasonably stable, and the reduction in HbA1c levels was relatively small.

ABEC Trial

3.31 In the ABEC trial, the insulin glargine (Lantus or Basaglar) was self-administered using a vial and syringe. The titration of the insulin glargine dose was patient-driven utilising instructional material provided by Eli Lilly (ABEC CSR, p42). Sites were responsible for consistent instruction of all enrolled patients with the materials provided. The patient-driven titration included the addition of 1 U of insulin daily until fasting blood glucose (FBG) reached ≤100 mg/dL (5.6 mmol/L). The investigators had the discretion of titrating the patient dose by more than 1 U daily during the visits if it was found to be necessary (ie, hyperglycaemia persisted despite appropriate patient titration). The investigators also had the discretion to decrease the dose only if it was noted that patients were experiencing hypoglycaemia.

3.32 During the 24 week treatment period patients visited the investigator site at weeks 0, 2, 4, 8, 12, 16, 20, and 24, and patients were contacted by telephone between the office visits.

3.33 Data are not recorded in the CSR for the period prior to the switch however, for inclusion in the ABEC trial patients were required to be receiving 2 or more oral antidiabetic agents (OADs) at stable doses for at least 12 weeks. Furthermore, patients were to have not used any other insulin except Lantus within the 30 days prior to entry, and were to not have had more than 1 episode of severe hypoglycaemia within the previous 6 months. Thus the trial included type 2 diabetes patients with stable disease.

3.34 The type 2 diabetes patients included in the ABEC trial are a subset of patients likely to be treated in clinical practice. Specifically, patients with a history of taking basal bolus therapy, patients likely to require mealtime insulin to achieve target control, and patients that had used short-acting glucagon-like peptide 1 (GLP-1) agonist (eg, exenatide) or long acting GLP-1 agonist (eg, liraglutide) within the previous 90 days were excluded from participating in the trial. Patients with significant comorbidities were also excluded.

3.35 The ABEC trial included patients that were (i) insulin naïve, (ii) treated with Lantus with adequate glycaemic control or (iii) treated with Lantus but had inadequate glycaemic control. Overall, 39.6% of patients were treated with Lantus at study entry. Only 5.8% of patients had a HbA1c of <7.0% at baseline, and 44.6% had a HbA1c ≥8.5% (AEBC CSR, Table ABEC.11.1). Thus it appears that the majority of patients in the ABEC trial had inadequate glycaemic control at study entry. For patients treated with Lantus at study entry, the insulin glargine dose (either as Lantus or Basaglar) was increased by a mean of 16-20 units/day, and the HbA1c decreased by a mean of approximately 1.0%, during the 24 week trial period (ABEC CSR, Table ABEC.11.11). Thus during the ABEC trial the patient's insulin glargine treatment was generally intensified compared with that prior to study entry.

<u>The impact of substitution on the collection of longer term evidence of safety</u>

3.36 The safety data from the ABEB and ABEC trials were reviewed by the PBAC at their March 2015 meeting. The PBAC considered that the claim of non-inferior comparative safety was adequately supported (PBAC minutes paragraph 7.2). The resubmission notes (p5) that establishing the comparative safety profile requires more experience than that gained within a clinical trial, and market experience with the biosimilar product is essential in order to detect rare events that cannot be detected in clinical trials. Immunogenicity is noted to be of particular concern. The resubmission (p6) and the March 2015 PBAC minutes (paragraph 6.16) quote the following from the Delegate's Overview for Basaglar, and it is noted that a pharmacovigilance plan is in place for Basaglar:

'[t]he 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.'

3.37 The resubmission considered (p6) that substitution of Lantus and Basaglar by the pharmacist could compromise pharmacovigilance, specifically the traceability to a particular form of insulin glargine could be compromised. It is noted that prescribers report significantly more adverse events (AEs) than pharmacists, and only pharmacists will have direct knowledge of the actual item dispensed. Further, the clinician may rely on assumed knowledge of the medicine used based on the original prescription. TGA AE reporting statistics for 2011 are presented in the resubmission (p6). Of the approximately 14,400 reports received by the TGA, 52% were from pharmaceutical companies, 12% from hospitals, 7% from General Practitioners, 18% from State and Territory Health Departments and 3% from consumers. The sources for other reports (8%) included community pharmacists and specialists. Lilly states that most of the AEs reported through their local pharmacovigilance programs are derived through sales representative interactions with prescribing health care professionals.

3.38 The "Blue Card" for AE reporting requests for the suspected medicine that the trade name is used and, if known, the batch number and AUST R or AUST L number is provided[14]. Given this a prescriber may source additional detail, including the trade name, from the patient and/or pharmacist. Table 1 provides the number of AEs reported with and without the trade name specified for insulin glargine, two oral antidiabetic agents with multiple generic brand available (metformin and gliclazide) and a biological with a biosimilar available (filgrastim).

Table 1: AEs reported with and without trade name from the Australian Database of Adverse Event Notifications (DEAN)

Medicine	Time period	AE Reports
Insulin glargine	1 January 2013 – 21 February 2015	Total: 85 reports Trade name specified (Lantus, Lantus Optiset, Lantus Solostar): 82 reports Trade name not specified: 3 reports
Metformin	1 January 2013 – 21 February 2015	Total: 182 reports Trade name specified: 76 reports Trade name not specified: 106 reports
Gliclazide	1 January 2013 – 21 February 2015	Total: 26 reports Trade name specified: 14 reports Trade name not specified: 12 reports
Filgrastim	1 January 2011[a] – 21 February 2015	Total: 20 reports Trade name specified (Neupogen, Nivestim): 11 reports Trade name not specified: 9 reports

a The first filgrastim biosimilar (Nivestim) was listed on 1 April 2011
Source: Database of Adverse Event Notifications (DEAN) – medicines; http://apps.tga.gov.au/PROD/DAEN/daen-entry.aspx, accessed 9-10 June 2015

[14] https://www.tga.gov.au/sites/default/files/problem-medicines-forms-bluecard-150218.pdf

3.39 As of 2012 European legislation mandates prescription of all biological medicinal products by brand name, as well as recording of the batch number of the product used[15]. Based on an analysis of 13,790 spontaneous adverse drug reaction (ADR) reports from the EU EudraVigilance over the period 2004-2010, brand names were recorded for 90.4% of biopharmaceuticals and for 96.2% of biopharmaceuticals when the biopharmaceutical was the suspected drug[16]. Batch numbers were rarely reported with the brand name and batch number reported for 3.8% of biopharmaceuticals and for 5.3% of suspected biopharmaceutical. However, this analysis predates the legislation mandating the recording of batch numbers.

3.40 A similar analysis of the Italian Spontaneous Reporting System Database over the period 2001-2013, reported that 94.8% of biological-related reports included an identifiable product name, whilst only 8.6% indicated the corresponding batch number.[17]

Substitutability of delivery devices

3.41 The resubmission quoted (p5) the following from the FDA's Guidance for Industry on Biosimilars: Q & As Regarding Implementation of the BPCI Act of 2009 :

> "Additional considerations apply for a proposed interchangeable product. For example, in reviewing an application for a proposed interchangeable product, the FDA may consider whether the differences from the reference product significantly alter critical design attributes, product performance, or operating principles, or would require additional instruction to healthcare providers or patients, for patients to be safely alternated or switched between the reference product and one or more interchangeable products without the intervention of the prescribing healthcare provider. Additional performance data about the delivery device may also be necessary".

3.42 The resubmission noted (p5) the Basaglar clinical trials did not test the possible safety implications of switching patients between Lantus and Basaglar delivery devices without the intervention of the prescribing healthcare provider.

3.43 The resubmission argued (p7) that '…differences between the disposable pens can create confusion and potentially compromise patient safety, and …. that there are significant risks associated with substitution between the different brands of cartridges'. More specifically, patients may receive a different device to the one they were trained on, or they may receive a cartridge that cannot be used with their current re-usable pen. It is further noted that with the Lantus Solostar pen patients are able to dial 80 units per injection whereas with the Basaglar Kwikpen patients are only able to dial 60 units per injection. Thus patients who require more than 60U per

[15] Ebbers HC and Chamberlain P. Interchangeability. An insurmountable fifth hurdle? GaBI Journal 2014; 3(2):88-93

[16] Vermeer NS et al. Traceability of Biopharmaceuticals in Spontaneous Reporting Systems: A Cross-Sectional Study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance Databases. Drug Saf 2013; 36:617–625

[17] Cutroneo PM et al. Safety Profile of Biological Medicines as Compared with Non-Biologicals: An Analysis of the Italian Spontaneous Reporting System Database. Drug Saf 2014; 37:961–970

day will need to inject twice with Basaglar, but possibly only once with Lantus. Or, if a second injection was required with Lantus, the number of units required to be dialled for the second injection when using Basaglar would be different to that when using Lantus. The resubmission considers that this could create significant confusion to the patients and could potentially lead to serious medication errors.

3.44 The resubmission appeared to be concerned that substitution will occur automatically and unchecked.

3.45 However, brand substitution has been occurring successfully for many years and there are well established guidelines and processes for substitution of 'a' flagged items, which clinicians, pharmacists and patients are familiar with.

3.46 As always, the prescriber has the option to offer patients the choice of taking the original brand or the substitute brand, or to indicate on the prescription that only the brand being prescribed must be dispensed. Similarly, the patient has the choice as to whether or not they wish to receive a substitute brand at the time of dispensing, if that option has been made available by the prescriber.

3.47 Further, professional societies such as the Pharmaceutical Society of Australia (PSA) provide guidelines to professional pharmacists which outline the conditions under which substitution is permitted and provide guidance on best practice for dispensing substitute pharmaceutical benefits. These include recommendations including that;[18]

- Where substitution is allowed and the patient is offered or enquires about alternate brands, the pharmacist and the patient should discuss the safety and suitability of alternate brands for that patient,
- Brand substitution may only occur after consultation with and agreement of the patient, and
- Where substitution is allowed, the pharmacist must provide thorough advice (including for example, differences in product presentation) whenever substitution occurs.

3.48 The PSA has also recently published a position statement on biosimilar medicines, in which it notes that pharmacists follow substitution principles which respect the choice of prescribers and patients. The statement affirms that patient safety is a prime concern of the pharmacy profession and notes that in relation to biosimilar medicines, risk assessment steps include assessment of safety and efficacy by the TGA, consideration by the PBAC and clinical assessment by the prescriber have been taken.[19]

3.49 In relation to insulin, many pharmacies stock and supply delivery devices, with pharmacists able to provide training to patients on their use. In addition, diabetes educators can discuss the available brands of insulin glargine and, if appropriate, instruct patients to request the pharmacist provide a specific brand or device.

[18] http://www.psa.org.au/download/policies/pbs-brand-substitution.pdf; accessed 19 June 2015

[19] https://www.psa.org.au/download/policies/biosimilar-medicines-position-statement.pdf, accessed 30 September 2015

3.50 Further, the Commonwealth has recently committed to the launch of a national campaign costing up to $20 million over three years to increase the awareness, understanding and uptake of biosimilar medicines.

3.51 There is currently a multiplicity of insulin brands and devices listed on the PBS with some insulins being available in five different brand/device combinations, not all of which are readily distinguishable at the brand name level (see examples in Table 2). The availability of the Basaglar devices as alternatives to the Lantus devices would not be expected to result in additional complexity to what is already being managed in practice.

Table 2: Examples of PBS listed insulin brand/device combinations

Listed Drug	Form	Manner of Administration	Brand	Responsible Person	Authorised Prescribor
Insulin Glulisine	Injection (human analogue) 100 units per mL, 10 mL	Injection	Apidra	SW	MP NP
	Injections (human analogue), cartridges, 100 units per mL, 3 mL, 5	Injection	Apidra	AV	MP NP
			Apidra SoloStar	SW	MP NP
Insulin Isophane	Injection (bovine) 100 units per mL, 10 mL	Injection	Hypurin Isophane	AS	MP NP
	Injection (human) 100 units per mL, 10 mL	Injection	Humulin NPH	LY	MP NP
			Protaphane	NO	MP NP
	Injections (human), cartridges, 100 units per mL, 3 mL, 5	Injection	Humulin NPH	LY	MP NP
			Protaphane InnoLet	NI	MP NP
			Protaphane Penfill 3 mL	NO	MP NP

Source: National Health (Listing of Pharmaceutical Benefits) Instrument 2012 (PB 71 of 2012); http://www.comlaw.gov.au/Details/F2015C00406, accessed 14 June 2015

3.52 At the March 2015 meeting, the PBAC considered "that any differences in the re-usable pen devices, can be managed in the course of the regular patient education and counselling on the use of the devices that is provided to patients by prescribers, pharmacists and diabetes educators, and that these differences were not sufficient to preclude marking the two brands as equivalent. Similarly, the PBAC considered that any differences in the pre-filled disposable pen devices can be managed in the course of the regular patient education and counselling." (PBAC minutes paragraph 7.7)

3.53 The PBAC reiterated this position at the July 2015 consumer meeting on biosimilars, stating that it considered that differences in drug delivery devices may be able to be managed in the course of the regular patient education and counselling on the use of the devices that is provided to patients by prescribers, pharmacists and other health care professionals, but that this would be considered on a case by case basis.

3.54 PBAC noted Lilly's continuing concerns regarding the substitutability of the delivery devices as set out in its pre-PBAC response. See also Section 4 – outcomes.

Therapeutic Goods Administration (TGA) and Advisory Committee for Prescription Medicines (ACPM) considerations

3.55 In considering what advice to give to the Minister on this matter, the PBAC took into account the materials concerning the TGA's consideration of Basaglar, including:

- The Basaglar Product Information;
- Email correspondence of 10-11 November 2014 between the TGA and Eli Lilly regarding the Health Care Professionals letter;
- the TGA letter to Eli Lilly dated 17 April 2015;
- Eli Lilly's Basaglar resubmission of April 2015, including the submissions in section 3 of that resubmission;
- the Department's overview for PBAC for insulin glargine, including the outcomes of the TGA review of the section of the Eli Lilly resubmission relevant to the TGA/ACPM's determination regarding substitutability as recorded at paragraphs 3.53 – 3.54 of that overview ; and
- the sponsors pre-PBAC response of October 2015.

3.56 The PBAC Minutes from March 2015 indicate that the PBAC considered that neither the TGA nor the ACPM made a determination regarding the pharmacist-level substitutability of Basaglar and Lantus. However, Eli Lilly's resubmission asserts that documentary evidence demonstrates that the TGA and/or the ACPM did indeed make a positive determination regarding the substitution of Basaglar and Lantus and required conditions of registration and PI wording, confirming Basaglar should only be substituted with Lantus under strict medical supervision.

3.57 The TGA subsequently wrote to Eli Lilly on 17 April 2015 to confirm its position that substitutability was not evaluated by the TGA and advice on whether or not the product was substitutable was not sought from ACPM.

3.58 The TGA has reviewed the section of the Eli Lilly resubmission relevant to the TGA/ACPM's determination regarding substitutability and has indicated that, consistent with the 17 April letter, it does not agree with the proposition that "the actions of the TGA and ACPM… evidence an active consideration of the issue, and positive determination that pharmacist-level substitution is not appropriate for Basaglar and Lantus, by the TGA and ACPM."

3.59 Rather, the TGA has confirmed its view that the material described by Eli Lilly in the resubmission, is consistent with the proposition that both the delegate and ACPM were adopting the approach outlined in the 2013 TGA guidance document (Evaluation of Biosimilars V1.0, July 2013), and not making a specific finding about

whether Basaglar could be substituted at the pharmacy level for Lantus. The TGA confirmed that the approved PI wording was intended to reflect the statements in the biosimilars guidance document generally, rather than being indicative of any specific conclusion in relation to Basaglar resulting from analysis, by the delegate or by ACPM, of data provided by Ely Lilly in relation to for the particular medicine. While the TGA acknowledges the email correspondence of 10-11 November 2014 regarding the possibility of the imposition of a condition in relation to a health care professional letter, it notes that no such condition was imposed on the registration of Basaglar.

The PBAC's power to make a finding regarding substitutability

3.60 The PBAC has always provided advice to the Minister regarding whether a brand or form of a medicine listed on the PBS should be substitutable for another brand or form of the same medicine at the time of dispensing. Examples of where this advice is provided include different brands and forms of both small chemical molecule and biological medicines.

3.61 At its March 2015 meeting, the PBAC considered a request for advice, pursuant to section 101(3) of the *National Health Act 1953* (NH Act), made to it by the Minister's delegate. That section of the Act provides:

"The Pharmaceutical Benefits Advisory Committee shall make recommendations to the Minister from time to time as to the drugs and medicinal preparations which it considers should be made available as pharmaceutical benefits under this Part and shall advise the Minister upon any other matter concerning the operation of this Part referred to it by the Minister."

3.62 The resubmission argued that, read in the context of the Therapeutic Goods Act 1989 (TG Act):

- s101 (3) of the NH Act does not permit the PBAC to find that two products are "equivalent" under section 84AJ of the NH Act if the TGA "has not made a positive determination regarding the safety and efficacy of allowing pharmacist level substitution of those products". It would seem to follow that that the Minister could not make a determination of equivalence in those circumstances; and
- (it follows from that, or even if that is wrong) the NH Act does not permit the Minister to determine or decide that two products are equivalent for the purposes of "a"-flagging, nor the PBAC to give advice to that effect, if the TGA has concluded that pharmacy-level substitution is unsafe or should not be permitted.

3.63 The resubmission argued the TGA is solely responsible, as part of considering whether or not to register a medicine in Australia, for determining matters concerning the safety and efficacy of the medicine.

(References in this context to conclusions of the TGA should be understood to mean the conclusions of the Secretary's delegate - usually an officer of the TGA - under the TG Act.)

3.64 In support of the argument made, the resubmission pointed to matters including the following:

- s25(1)(d) of the TG Act requires the TGA to consider matters of quality, safety and efficacy when determining whether to register a product on the ARTG;
- the PBAC is established under s100A of the NH Act to assess whether certain drugs ought to be made available under the PBS;
- the distinction between the PBAC's economic focus and the TGA's safety focus is made clear in the two Acts' regulation of the eligibility for membership to, and the functions of, the respective bodies. This includes the detailed requirements in the TG Act regarding the clinical and other data to be furnished to, and complex evaluation of safety evidence to be undertaken by, the TGA.

3.65 Subsequent to this resubmission being made, legislation passed by the Parliament on 23 June 2015 made a technical amendment to the NH Act related to the PBAC function for recommending schedule equivalence to the Minister, and the Minister's power to determine schedule equivalence:

3.66 Under subsection 85(6A) of the NH Act commencing 1 November 2015, "If the Minister determines a brand of a pharmaceutical item under subsection (6), the Minister may, by legislative instrument, determine that, for the purposes of paragraph 103(2A)(b), the brand is to be treated as equivalent to one or more other brands of pharmaceutical items."

3.67 Under subsection 85(6B) of the NH Act commencing 1 November 2015, " In deciding whether the brand of pharmaceutical item is to be treated as equivalent to one or more other brands of pharmaceutical items, the Minister must have regard to any advice given by the Pharmaceutical Benefits Advisory Committee."

3.68 Under subsection 101(4AACD) of the NH Act, commencing 1 November 2015, "The Pharmaceutical Benefits Advisory Committee may give advice to the Minister in relation to whether or not the Minister should determine that a brand of a pharmaceutical item is to be treated as equivalent to one or more other brands of pharmaceutical items."

3.69 Neither section 85(6A) or 85(6B) of the NH Act require that, prior to two pharmaceutical benefits being marked as equivalent in the Schedule of Pharmaceutical Benefits, any advice, let alone positive advice, must first be obtained from the TGA that the two pharmaceutical benefits are substitutable.

3.70 Nor does section 101(4AACD) of the NH Act, which empowers the PBAC to give advice to the Minister, make any reference to the TG Act.

3.71 The Department considers that:

- substitutability of brands or forms of the same medicine (drug) is a matter which may or may not be examined by the TGA in the course of assessing whether a particular brand or form of that medicine should be registered;

- if the TGA has not considered substitutability, that does not prevent the Minister from deciding that the two pharmaceutical benefits should be "a"-flagged, nor the PBAC from giving advice to the Minister about whether that should happen;
- if the TGA has considered substitutability, then any views expressed by the TGA about that are matters which the Minister is permitted to, and would be likely to wish to, take into account when deciding whether or not two pharmaceutical benefits should be "a"-flagged. Similarly, they would be matters which the PBAC, if advising the Minister, would be permitted to take into account.

3.72 In understanding the PBAC's and the Minister's powers it is of relevance to recall that:

- the primary implications of an "a"-flagging decision relate to an offence in the context of the supply of a pharmaceutical benefit as part of a Commonwealth subsidy scheme;
- the decision as to whether, in any particular case, an "a"-flagged pharmaceutical benefit will be substituted, remains in the hands of prescribers and pharmacists; and
- an "a"-flagging decision does not prevent a prescriber or pharmacist from deciding that, for any particular patient, switching between the two "a"-flagged pharmaceutical benefits is not safe.

3.73 The "a"-flagging of two pharmaceutical benefits in the Schedule of Pharmaceutical Benefits, as a matter of law simply has the effect that it is not an offence for a pharmacist, in certain circumstances, to supply under the PBS a particular pharmaceutical benefit (the substitute benefit) even though another pharmaceutical benefit was prescribed. It will be an offence for the pharmacist to do that if:

- the prescriber indicated that only the pharmaceutical benefit referred to in the prescription could be supplied; or
- the supply of the substitute benefit is prohibited in the state or territory where it is to be supplied.

3.74 "A"-flagging does not require substitution for all patients, nor permit substitution where a prescriber has considered that not to be appropriate.

3.75 Even where two pharmaceutical benefits are "a"-flagged, it is up to the relevant prescriber and pharmacist to determine whether substitution is appropriate. Both of those health professionals will have regard to the individual patient's circumstances to consider whether substitution is appropriate and may:

- in the case of the prescribing physician, elect to write the prescription so as to indicate that substitution by the pharmacist is not permissible; or
- in the case of the pharmacist, elect not to dispense the 'substitute' pharmaceutical benefit.

3.76 The fact that individual patient safety concerns remains an issue for the pharmacist to consider, even where two pharmaceutical benefits are "a"-flagged, is reflected in the PSA's "Dispensing Practice Guidelines and Guidelines for Pharmacists on PBS Brand Substitution". Those documents contain the following statements:

- "Where there is a potential option for brand substitution, a discussion of the rationale should take place if the patient desires. Following a full disclosure of the choices, the pharmacist should be satisfied that the patient understands the outcome. Details of the substitution should be recorded if substitution takes place and noted on the prescription";
- "Consumer Medicine Information leaflets should be provided on initiation of any treatment, and offered on subsequent dispensings according to established guidelines."
- "Brand substitution may only occur after consultation with and agreement of the patient (or the carer), and if the prescriber has not indicated on the prescription, "no substitution", or equivalent.
- Where substitution is allowed and the patient is offered or enquires about alternate brands, the pharmacist and the patient should discuss the safety and suitability of alternate brands for that patient.
- The patient's health should always be the pharmacist's prime consideration in any brand substitution decision. Decisions to substitute one brand for another should not place patients at risk.
- Pharmacists should endeavour to be consistent in the selection of brands for patients on long-term therapy in order to avoid patient confusion. If this is not possible then the patient should be consulted."

3.77 The pre-PBAC response noted that subsequent to Lilly's resubmission, legislation was passed to amend the NH Act related to the PBAC function for recommending schedule equivalence to the Minister, and the Minister's power to determine schedule equivalence.

3.78 The pre-PBAC response asserts that "in providing legitimate advice to the Minister on the question of substitutability, the PBAC cannot disregard issues of safety and efficacy, which are matters assessed by the TGA, ACPM and Secretary's delegate related to the statutory obligation under section 25(1)(d) of the TG Act. The evidence indicates that the Secretary's delegate made a decision to register Basaglar on the basis that pharmacy-level substitution should not be permitted and should only otherwise occur under strict medical supervision. If the PBAC disregards the decision of the Secretary's delegate and recommends to the Minister that Basaglar and Lantus ought to nevertheless be regarded as equivalent, then the PBAC would likely fall into administrative error, having failed to take relevant considerations into account in making its recommendation.

3.79 As noted above in paragraphs 3.54 to 3.58, the PBAC has taken into account, in the course of considering the resubmission, the views of the TGA (including the Secretary's delegate).

4 PBAC Outcome

4.1 The PBAC reaffirmed its March 2015 advice to the Minister that the Basaglar and Lantus brands of insulin glargine cartridges, and the Basaglar KwikPen and Lantus Solostar brands of insulin glargine pre-filled disposable pens respectively, could be marked as equivalent in the Schedule of Pharmaceutical Benefits for the purposes of substitution by the pharmacist at the point of dispensing.

4.2 The PBAC noted the sponsor's concerns about safety of substitution and risk to pharmacovigilance as set out in the resubmission and pre-PBAC response. The PBAC considered that these concerns could be addressed, in part because the substitution of medicines in Australia is not "automatic". Substitution at the point of dispensing is performed only in consultation with, and with the consent of, the patient. The submission claimed that pharmacovigilance accuracy would be negatively impacted because only pharmacists would have direct knowledge of the actual item dispensed, however the PBAC considered that as substitution is performed in consultation with the patient, the patient would also have knowledge of the brand dispensed. The PBAC noted that there may be a role for the eHealth record in the collection of this information to aid with pharmacovigilance.

4.3 The PBAC noted that there are professional guidelines on substitution issued by the Pharmaceutical Society of Australia and that the Pharmacy Guild of Australia has also produced a policy position on biosimilars and substitution that emphasise patient safety and consultation.

4.4 The PBAC noted that the prescriber has the option to offer patients the choice of taking the original brand or the substitute brand, or to indicate on the prescription that only the brand being prescribed must be dispensed. Similarly, the patient has the choice as to whether or not they wish to receive a substitute brand at the time of dispensing, if that option has been made available by the prescriber.

4.5 The PBAC noted the sponsors concern that doctors are more often reporters of adverse drug reactions (ADRs) and that they will use their prescribing records for reporting. The PBAC noted that the TGA ADR reporting system requests the trade name of the medicine, and additionally the batch and AUSTL or AUSTR numbers if known. The PBAC agreed that community pharmacists may not be as frequent reporters of ADRs, however considered that with the education and promotion being undertaken for biosimilars, there was opportunity to enhance pharmacovigilance by pharmacists.

4.6 The PBAC noted that the Solostar delivery device for Lantus can deliver a higher dose, 80 units, than the Kwikpen device for Basalgar, 60 units. The PBAC considered that the proportion of patients requiring a dose in the range between 60 and 80 units was small, and that in other aspects, the pen delivery devices were similar. The PBAC further noted that the actual devices are not routinely provided by pharmacies, but by clinicians and diabetes educators. The PBAC considered this would likely reduce the occasions on which pharmacy level substitution can occur without the involvement of the clinician or diabetes educator. The PBAC therefore reaffirmed its view that any differences in the re-usable pen devices, can be managed in the course of the regular patient education and counselling on the use of the devices that is provided to patients by prescribers, pharmacists and diabetes educators, and that these differences were not sufficient to preclude marking the two brands as equivalent.

4.7 The PBAC also noted an Australian study (Kalisch et al 2009) that found that the number of pharmacies attended by a patient was the factor most likely to increase odds of multiple brand substitution. The PBAC noted that most pharmacies do not

stock a large range of insulins (given the high cost, large number of brands and forms available, and the requirement for refrigeration) and considered that patients who require insulin glargine are more likely to utilise a single pharmacy that orders stock specifically for that patient.

4.8 The PBAC reiterated 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.

Outcome:
The PBAC reaffirmed its March 2015 advice to the Minister that the Basaglar and Lantus brands of insulin glargine cartridges, and the Basaglar KwikPen and Lantus Solostar brands of insulin glargine pre-filled disposable pens respectively, could be marked as equivalent in the Schedule of Pharmaceutical Benefits for the purposes of substitution by the pharmacist at the point of dispensing.

5 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.

6 Sponsor's Comment

The sponsor disagrees with the PBAC's recommendation to reaffirm the March 2015 advice to the Minister to 'a'-flag Basaglar and Lantus brands of insulin glargine. We remain concerned that the evidence base for Basaglar does not support substitution at the pharmacy level and that the regulatory and cost effectiveness processes together created yet-unresolved conflicts between the TGA and PBAC requirements for Basaglar that make it difficult to proceed with a listing till they are sufficiently resolved.