Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Insulin glargine

Proprietary Product Name: Abasria / Abasria KwikPen[1]

Sponsor: Eli Lilly Australia Pty Ltd

August 2015

TGA Health Safety Regulation

[1]With a subsequent application, which followed the TGA's evaluation and approval of this application, the registered names were amended on the Australian Register of Therapeutic Goods (ARTG) to:

- Basaglar KwikPen insulin glargine (rbe) 100 IU/mL solution for injection cartridge ARTG 2155552
- Basaglar insulin glargine (rbe) 100 IU/mL solution for injection cartridge ARTG 215551.

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACE	angiotensin converting enzyme
ALAT	alanine aminotransferase
ASR	annual safety report
CCDS	company core data sheet
CHMP	Committee for Medicinal Products for Human Use
DCCT	Diabetes Control and Complications Trial
DSUR	development safety update report
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GLP-1	glucagon-like peptide-1
GPRD	General Practice Research Database
GW	gestational week
HMEC	human mammary epithelial cells
HIV	human immunodeficiency virus
IBD	international birth date
ICH	International Conference on Harmonisation
L6-hIR	L6 myoblasts from ATTC transfected with human insulin receptors
MAH	market authorisation holder
MAOI	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
NPH	neutral protamine Hagedorn
NYHA	New York Heart Association

Abbreviation	Meaning
PD	pharmacodynamics
PK	pharmacokinetics
PSUR	periodic safety update report
PT	preferred term
PYE	patient years of exposure
RR	reporting rate
RMP	risk management plan
RSI	request for supplementary information
SmPC	summary of product characteristics
SMQ	standardised MedDRA query
TZD	thiazolidinedione
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	Biosimilar (Insulin analogue)
Decision:	Approved
Date of decision:	10 November 2014
Active ingredient(s):	Insulin glargine
Product name(s):	Abasria, Abasria KwikPen[2]
Sponsor's name and address:	Eli Lilly Australia Pty Ltd 112 Wharf Road, West Ryde, NSW 2114
Dose form(s):	Solution for injection
Strength(s):	100 U/mL
Container(s):	Cartridge and prefilled pen
Pack size(s):	1, 2, 5 and 10
Approved therapeutic use:	*Insulin glargine 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.*
Route(s) of administration:	Subcutaneous (SC) injection
Dosage:	Adjusted to the individual patient.
ARTG number (s):	215551 and 215552

Product background

This AusPAR describes the application by the sponsor Eli Lilly Australia Pty Ltd to register Abasria, containing insulin glargine as the active ingredient, as a biosimilar. The proposed indications

> *Once-daily subcutaneous treatment of Type 1 diabetes in adults and children and Type 2 diabetes mellitus in adults who require insulin for the control of hyperglycaemia*

match those of the reference product, Lantus®. The strength of the active ingredient (100 IU/mL) is the same and the excipient profile is similar to that of Lantus®, except that

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- Basaglar KwikPen insulin glargine (rbe) 100 IU/mL solution for injection ARTG 2155552 cartridge and
- Basaglar insulin glargine (rbe) 100 IU/mL solution for injection cartridge ARTG 215551.

zinc oxide is used in this product instead of zinc chloride; the resultant concentration of zinc ion (Zn^{2+}) is however identical.

Insulin glargine is 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.

The approval sought is for adults, adolescents, and children 2 years and above.

Abasria is proposed for marketing in 2 presentations:

- a 3 mL cartridge, for delivery by a compatible CE-marked reusable pen injector, and
- the same 3 mL cartridge sealed in a prefilled pen injector (KwikPen).

The pack sizes and pen injectors differ from those available to administer Lantus (Sanofi-Aventis) cartridges but are appropriate for use with Eli Lilly insulin cartridges.

Long-acting insulin analogues, such as insulin glargine, provide smooth, peakless basal insulin profiles. The putative benefits over agents such as neutral protamine Hagedorn (NPH) include reduced frequency of hypoglycaemia and better fasting blood glucose control.

Under the EU guidelines (see below), the primary role of Phase III clinical studies is to assess immunogenicity.

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.

The Biosimilar Medicinal Products Working Group (BMWG) produced a concept paper for revision of the guideline in 2011; and a revised guideline was produced[3], with a deadline for comments set as 31 July 2014. The TGA evaluated biosimilarity using this adopted guideline which states '*acceptance of claim of biosimilarity means the product can be marketed and prescribed by medical practitioners. '* Substitution by the pharmacist without consulting the treating medical practitioner is not addressed in the relevant adopted EMA Guidelines.

The TGA also followed the guideline 'Evaluation of biosimilars, Version 1.0, TGA July 2013' when evaluating this submission. This guideline stated at the time of the evaluation that:

> '*As biosimilars are not generic versions of their reference products, to inform the prescriber the text of the PI should include words to the effect of:*
>
> > *'The comparability of [biosimilar product name] with [Reference product name (AustR nnnnnn)] has been demonstrated, with regard to particular physicochemical characteristics and efficacy and safety outcomes [see PHARMACOLOGY and CLINICAL TRIALS]. The level of comparability that has been shown supports the use of [biosimilar product name] for the listed indication[s]. The level of comparability that has been shown is not sufficient to designate this product as a generic version of [Reference product name]. Replacement of [Reference product name] with [biosimilar product name], or vice versa, should take place only under the supervision of the prescribing medical practitioner*.'
>
> as the first paragraph under *Precautions'.*

[3] EMEA/CHMP/BMWP/32775/2005_Rev.2 Draft guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues

This TGA guideline is currently under review.

CHMP released an insulin-specific guideline in 2006.[4] Two particular issues that the insulin guidelines[4] seek to address are:

1. *Hypoglycaemia* (possibly caused by differences in activity of different brands). PK and PD (euglycaemic clamp) studies are required to show that the efficacy of the biosimilar insulin is predictable and consistent.
2. Immunogenicity. The draft guidance states that 'the issue of immunogenicity can only be settled through clinical trials of sufficient duration, that is, at least 12 months using subcutaneous administration, with a 6-month comparative phase to be completed pre-approval while data at the end of 12 months could be presented as part of the post-marketing commitment.' The sponsor should also design a pharmacovigilance program that will rapidly detect any clinically significant immunogenicity that may emerge over extended time periods.

The following three EU guidelines which have been adopted by the TGA are also relevant to this application:

- Guideline On Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance: Non-Clinical And Clinical Issues (EMEA/CHMP/BMWP/42832/2005)
- Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ 2010)
- Guideline On Immunogenicity Assessment Of Biotechnology-Derived Therapeutic Proteins (EMEA/CHMP/BMWP/14327/2006).

Regulatory status

The product has not been registered in Australia.

Abasria is the first biosimilar version of the long-acting insulin analogue, insulin glargine (Lantus; Sanofi-Aventis), which was first registered in Australia in 2001.

Although insulin-specific guidelines have been in place in Europe since 2006, no biosimilar insulin has been registered in Europe or Australia. Three products were submitted (biosimilars of Humalog) to the European medicines Agency (EMA) in 2007 (from the MJ Group, Mumbai, India) but all were withdrawn in 2008 prior to opinion. Concerns included, inter alia, the lack of euglycaemic clamp studies, differential loss to follow-up in the Phase III study and inadequacies in the assessment of immunogenicity in the Phase III study.[5]

At the time the TGA considered this application (in 2014), a similar application had been approved in the European Union (EU) and was under consideration in the USA.

Table 1: International regulatory status (as at September 2014)

Country	Decision	Approved indication
USA	Under consideration.	Not applicable.

[4]EMEA/CHMP/BMWP/32775/2005 Rev 1. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues
[5]European Medicines Agency. Press release: Marvel Life Sciences Ltd withdraws its marketing authorisation applications for Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel. 16 January 2008. EMEA/2435/2008. London: EMA, 2008

Country	Decision	Approved indication
European Union (EU)	Approved 9 September 2014.	*Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.*

Product information

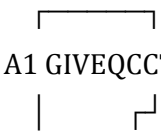
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug substance (active ingredient)

Insulin glargine is a 2-chain peptide containing 53 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 32 amino acids. As in human insulin, insulin glargine contains 2 interchain disulfide bonds and one intrachain disulfide bond. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and 2 arginines are added to the C-terminus of the B-chain. The drug substance has the following structure:

Figure 1: Structure



The amino acid sequence of this product is the same as that of Lantus.

Synthesis of the gene and vector, development and characterisation of the cell line were satisfactorily described and validated. Cell banking processes are satisfactory.

The fermentation processes are at large scale but are relatively simple. The monitoring and acceptance criteria satisfactorily control the quality and consistency of the harvest. Purification is relatively intensive and complex. The acceptance criteria for the various steps and the drug substance specifications adequately control the quality and consistency of the drug substance.

All characteristics of the product of the product were investigated with multiple orthogonal techniques. These confirmed the expected primary, secondary and tertiary structure. Bioactivity was demonstrated by multiple in vitro and in vivo methodologies. Impurities were low and adequately controlled.

Appropriate validation data have been submitted in support of the test procedures; that is, the proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use.

Drug product

The drug product, Abasria 100 U/mL solution for injection is a clear and colourless solution supplied in a 3 mL glass cartridge with elastomeric disc seal and plunger for administration via subcutaneous injection. It is supplied as a cartridge or as a Kwikpen in packs of 1, 2, 5 or 10. The formulation includes glycerine, metacresol and zinc oxide.

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product were submitted.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data indicate the product is not photostable.

The proposed shelf life is 12 months when stored at 2 to 8°C.

In-use stability data have also been submitted. The proposed shelf life and storage conditions after first use are 28 days when stored at less than 30°C.

The stability data also allow excursions from storage conditions of up to 25°C for 21 days during shipping.

Biopharmaceutics

Pharmacokinetic data following a single subcutaneous injection have been submitted and all issues resolved.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The quality evaluator recommends that Abasria (insulin glargine (rbe)) solution for injection in cartridge and prefilled pen 100 U/mL should be approved with the following conditions of registration:

1. *Batch release testing by the TGA*

   It is a condition of registration that, as a minimum, the first five independent batches of Abasria (insulin glargine (rbe)) solution for injection in cartridge and prefilled pen 100U/mL) imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA. This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency.

2. *Certified Product Details*

   An electronic draft of the Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

III. Nonclinical findings

Introduction

The nonclinical submission contained comparative studies on primary pharmacology and repeat-dose toxicity. The scope of the nonclinical program was in accordance with the relevant TGA adopted EU guideline.[6]

EU and USA sourced batches of Lantus® were used as the comparator (reference) product in separate experiments/studies.

Pharmacology

No statistically significant differences were identified between the form of insulin glargine in Abasria ('LY2963016') and that in Lantus® in in vitro assays examining:

- binding affinity for recombinant human insulin receptors and the human IGF-1 receptor;
- metabolic activity (assessed as stimulation of lipogenesis in mouse adipocytes); and
- mitogenic potency (assessed in rat and human cell lines with varying relative IGF-1 receptor : insulin receptor expression levels).

A statistically significant difference was observed between Abasria and Lantus® forms of insulin glargine by pairwise analysis in assays examining stimulation of human insulin receptor auto-phosphorylation. The magnitude of the difference, with the Abasria form being approximately 22% more potent, is not so large as to indicate a difference that is likely to be biologically significant. Furthermore, the finding was not confirmed in a second similar study or evident in the other assays. The sponsor also raised the absence of statistical significance after allowing for multiple comparison adjustment, reflecting that native human insulin and another analogue (AspB10) were also employed in the assays. This is not a compelling argument given that these additional comparisons are not necessary to establish the comparability of the sponsor's form of the drug and the reference product and they only act to diminish the sensitivity of the assays to reliably detect small differences in activity between the two. The studies are considered to have established pharmacological comparability.

No specialised in vivo pharmacology assay was conducted (consistent with the applicable guideline) but relevant information was obtained as part of the toxicity studies conducted in rats, with the Abasria and Lantus® forms of insulin glargine shown to display comparable glucodynamic profiles following SC administration.

Pharmacokinetics

Toxicokinetic data in rats showed comparable systemic exposure following SC administration of the Abasria and Lantus® forms of insulin glargine. Bioequivalence in humans was claimed.

[6] Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues. Guidance on Similar Medicinal Products Containing Recombinant Human Insulin EMEA/CHMP/BMWP/32775/2005

Toxicology

Repeat-dose toxicity studies of 4 weeks duration were conducted in rats. These were performed according to Good Laboratory practice (GLP), involved once daily injection by the clinical (SC) route, and featured comprehensive histopathological examination. Group sizes were appropriate. Dose selection was generally appropriate; the high dose level selected in the first study (comparing Abasria to US-sourced Lantus®; 3 mg/kg/day) required lowering during the course of the study (to 2 mg/kg/day) due to excessive mortality. Systemic exposure in groups of animals treated with the Abasria form of insulin glargine ranged from 44 to 404 times (in terms of serum peak concentration (C_{max})) and 8 to 171 times (in terms of serum area under the serum concentration versus time curve (AUC_{0-24h})) that obtained in humans following administration of a 0.6 IU/kg dose.

Notable findings in the studies comprised:

- mortality, occurring secondary to hypoglycaemia;
- increased body weight gain, which was accompanied by increased food consumption (to compensate for reduced glucose levels); and
- histopathological changes in the
  - sciatic nerve (axonal degeneration)
  - skin and SC injection sites (increased adipose tissue), and
  - pancreas (decreased cytoplasm/ vacuolation of islet cells, consistent with atrophy).

These findings are consistent with the pharmacological activity of insulin[7] and were minimal or absent at the low-dose level (0.3 mg/kg/day), which yielded a high multiple of the clinical exposure.

The nature, incidence and severity of findings with Abasria® were comparable to those observed with both EU and US sourced Lantus®.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3.[8] This matches the existing category for Lantus® and is considered appropriate.

[7]Yasaki S. and Dyck PJ. (1990) Duration and severity of hypoglycemia needed to induce neuropathy. *Brain Res.* 531:8–15.
Sugimoto K., Baba M., Suda T., Yasujima M. and Yagihashi S. (2003) Peripheral neuropathy and microangiopathy in rats with insulinoma: association with chronic hyperinsulinemia. *Diabetes Metab. Res. Rev.* 19:392–400.
Géloën A., Collet A.J., Guay G. and Bukowiecki L.J. (1989) Insulin stimulates in vivo cell proliferation in white adipose tissue. *Am. J. Physiol.* 256:C190–C196.
Fujikura J., Fujimoto M., Yasue S., Noguchi M., Masuzaki H., Hosoda K., Tachibana T., Sugihara H. and Nakao K. (2005) Insulin-induced lipohypertrophy: report of a case with histopathology. *Endocr. J.* 52:623–628.
Blume N., Skouv J., Larsson L.I., Holst J.J. and Madsen O.D. (1995) Potent inhibitory effects of transplantable rat glucagonomas and insulinomas on the respective endogenous islet cells are associated with pancreatic apoptosis. *J. Clin. Invest.* 96:2227–2235.
Koranyi L., James D.E., Kraegen E.W. and Permutt M.A. (1992) Feedback inhibition of insulin gene expression by insulin. *J. Clin. Invest.* 89:432–436

[8]Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Nonclinical summary and conclusions

- The nonclinical dossier contained comparative studies on primary pharmacology and repeat-dose toxicity. The scope of the nonclinical program complies with the relevant EU guideline.
- Comparability between the form of insulin glargine in Abasria® and the form of the drug in EU and US sourced batches of Lantus® was shown in terms of pharmacological activity (receptor binding affinity and functional activity in cell-based assays; glucodynamic profile in vivo in rats) and toxicity profile (assessed in 4 week, GLP-compliant studies in rats).
- The ability of the nonclinical studies to support comparability to Australian Lantus® depends on the conclusion of the quality evaluator regarding the identity of Lantus® products across jurisdictions. Provided that EU and/or US sourced Lantus® is considered to be identical or highly comparable to the Australian product, there are no nonclinical objections to the registration of Abasria for the proposed indications.
- The nonclinical evaluator also recommended amendments to the draft PI document but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

Introduction

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

The rationale for the drug development program is stated by the sponsor as:

> *'The development plan for Abasria, informed by the scientific principles set forth in the Committee for Medicinal Products (CHMP) guidances on biosimilars and adopted by the TGA, reflects a stepwise approach to demonstrating the similarity of ABASR1A to the reference medicinal product (Lantus). The aim of the Abasria development program was to demonstrate that Abasria has a highly similar profile to Lantus in terms of quality, nonclinical, pharmacokinetics and pharmacodynamics, and clinical safety and efficacy aspects, allowing Abasria to adopt the data generated with Lantus and thus the Australian Product Information (AUPI) for Lantus.'*

The drug development program is described in these terms:

> *'The totality of data presented in this application, specifically the clinical data summarised in Module 2, support a sufficient demonstration of similarity of Abasria to Lantus:*
>
> *The primary goal of the development program was achieved: Comparative PK and PD studies demonstrated highly similar PK and PD of Abasria to Lantus (Study ABEA) and of EU-approved Lantus to US-approved Lantus (Study ABEN) within predefined bioequivalence acceptance limits.*
>
> *Study ABEN established a scientific bridge that justified presenting the analyses of clinical efficacy and safety with a comparator group comprising EU- and US approved Lantus in the multinational Phase III clinical studies (ABEB and ABEC). The scientific bridge was supported by subgroup analyses in the Phase III studies comparing the treatment effect of Abasria to either EU- or US-approved Lantus for*

selected efficacy and safety parameters, which showed no clinically meaningful differential treatment effects between Abasria and Lantus (irrespective of source).

Clinical data from Studies ABEB (T1DM) and ABEC (T2DM) provide evidence that Abasria and Lantus have equivalent efficacy by meeting the primary test of the noninferiority of ABASR1A to Lantus as well as the secondary, complementary test of the noninferiority of Lantus to Abasria with respect to change in HbA1c, and with no statistically significant difference between treatment groups for key secondary measures of efficacy.

Clinical safety data from the Phase III studies demonstrate a highly similar safety profile (including immunogenicity, allergic reactions, and hypoglycemia) of Abasria to Lantus. Importantly, the development of anti-insulin glargine antibodies (as measured by TEAR) was not associated with any detrimental effect on efficacy and safety outcomes in patients with 11DM or T2DM.'

Comment: As is evident from the submission, the drug development program was informed by discussions with the FDA and with the EMA.

Guidance

Adopted guidelines and statements apply to this submission.

- EMEA/CHMP/BMWP/32775/2005 Annex To Guideline On Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance: Non-Clinical And Clinical Issues Guidance On Similar Medicinal Products Containing Recombinant Human Soluble Insulin.
- Guideline On Similar Biological Medicinal Products Containing

  Biotechnology-Derived Proteins As Active Substance:

  Non-Clinical And Clinical Issues
- Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ 2010) (CHMP 2010 Guideline on Immunogenicity Assessment Of Biotechnology-Derived Therapeutic Proteins).
- Guideline On Immunogenicity Assessment Of Biotechnology-Derived

  Therapeutic Proteins
- Evaluation of biosimilars Version 1.0, TGA July 2013 (now under review).

Contents of the clinical dossier

The submission contained the clinical information as outlined in the table above.

- five clinical pharmacology studies, all of which generated pharmacokinetic data and also pharmacodynamic data.
- no population pharmacokinetic analyses.
- one pivotal efficacy/safety study (ABEC).
- no dose-finding studies.
- one other efficacy/safety study (ABEB).
- Literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice (GCP)

As appended to the letter of application:

> *'I certify that Eli Lilly Australia Pty. Limited is in possession of documentation to demonstrate that the clinical studies accompanying the letter of 01 October 2013 were carried out in accordance with the principles of the Declaration of Helsinki and, if conducted in Australia, in accordance with the NH&MRC 'Statement on Human Experimentation'.*
>
> *I further certify that such documentation will be provided to the Department of Human Services and Health within three months of any request.*
>
> *I understand that the documentation referred to includes Ethics Review Committee approval letters, signed subject consent forms and the patient information sheet if there is one.'*

The evaluator mentioned in the discussion of each study any relevant matters in regard to GCP, ethical certification and auditing. In brief, no major concerns were noted but some clarifications from the applicant might be needed.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 2 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 2. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK- Single dose	ABEA ABEM ABEI	PK & PD PK & PD PK & PD
	Multi-dose		
	Bioequivalence† - Single dose	ABEN ABEA ABEM ABEI	PK & PD of Lantus US v. Lantus EU PK comparisons PK comparisons PK comparisons
	- Multi-dose	Not submitted.	
	Food effect	Not applicable.	
PK in special populations	Target population - Single dose	ABEE	PK & PD

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects with Type 1 Diabetes Mellitus (T1DM).

None of the pharmacokinetic studies in healthy volunteers had deficiencies that excluded their results from consideration. However, some studies are considered to be less relevant than others for the reasons briefly stated in Table 3.

Table 3 lists pharmacokinetic results that are considered to be less relevant due to study deficiencies.

Table 3. Pharmacokinetic results excluded from consideration.

Study ID	Subtopic(s)	PK results excluded
ABEE	Pharmacodynamics of Abasria Compared to Lantus® in Subjects with Type 1 Diabetes Mellitus	All results – assay insensitivity led to incomplete characterisation of the PK attributes of Abasria in this study.

The design of ABEE is briefly described in the tabulation below. The study did generate useful pharmacodynamic data.

Table 4: Design of study ABEE

Identifier; Study Type; Location; Status; Report Type	Primary Objective(s)	Design; Control Type	Test and Control Drug(s); Dose, Route, Regimen	Number of Subjects	Diagnosis or Inclusion Criteria	Treatment Duration
I4L-MC-ABEE; Patient PD; Section 5.3.4.2; Complete; Full CSR	Assess the duration of action of LY2963016 compared to LANTUS® in subjects with T1DM.	Phase 1, single-site, randomized, subject- and investigator-blind, single-dose, 2-period, crossover, 42-hour postdose, euglycemic clamp study.	Test: LY2963016; Single 0.3-U/kg dose, administered SC. Control: EU-approved LANTUS®; Single 0.3-U/kg dose, administered SC.	20 randomized 20 completed	Males and females, aged between 18 and 60 years, inclusive, with T1DM for ≥1 year, HbA1c ≤10.0%, fasting C-peptide ≤0.3 nmol/L, and BMI ≤29 kg/m^2.	Two 2-day treatment periods, with a washout from 7 to 21 days between treatment periods.

Evaluator's conclusions on pharmacokinetics

An important assumption that this evaluator makes is that the analytical method will be found to be satisfactory by the chemistry evaluator.

The Phase I studies marginally address the requirements of the adopted EU guideline EMEA/CHMP/BMWP/32775/2005 annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance:

Non-clinical and clinical issues - Guidance on similar medicinal products containing recombinant human soluble insulin,

> *'The relative pharmacokinetic properties of the similar biological medicinal product and the reference medicinal product should be determined in a single dose crossover study using subcutaneous administration. Comprehensive comparative data should be provided on the time-concentration profile (AUC as the primary endpoint and Cmax, Tmax, and T1/2 as secondary endpoints). Studies should be performed preferably in patients with type1 diabetes. Factors contributing to PK variability e.g. insulin dose and site of injection / thickness of subcutaneous fat should be taken into account.'*

The Phase I studies used consistent methods and appear to have been conducted diligently. The one study in subjects with Type 1 Diabetes Mellitus (T1DM) (Study ABEE) yielded uninterpretable PK results. Hence the useful data came from studies in healthy volunteers – the analytical method required C-peptide correction; the assay method was not specific to insulin glargine and its principal metabolite.

C-peptide correction is essential in studies involving healthy volunteers and it is accord with the need to have some form of baseline correction as articulated in the adopted guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Guideline On The Investigation Of Bioequivalence

Sampling times

'A sufficient number of samples to adequately describe the plasma concentration-time profile should be collected. The sampling schedule should include frequent sampling around predicted tmax to provide a reliable estimate of peak exposure. In particular, the sampling schedule should be planned to avoid Cmax being the first point of a concentration time curve. The sampling schedule should also cover the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure which is achieved if AUC(0-t) covers at least 80% of AUC(0-∞). At least three to four samples are needed during the terminal log-linear phase in order to reliably estimate the terminal rate constant (which is needed for a reliable estimate of AUC(0-∞))…'

'For endogenous substances, the sampling schedule should allow characterisation of the endogenous baseline profile for each subject in each period. Often, a baseline is determined from 2-3 samples taken before the drug products are administered…'

It is noted that the studies did not always achieve enough duration of sampling to achieve 80% of AUC from time 0 to infinity ($AUC_{(0-\infty)}$). The extrapolation of AUC exceeded 20% in ABEA, ABEI, ABEM and ABEN.

> *'Endogenous substances*
>
> *If the substance being studied is endogenous, the calculation of pharmacokinetic parameters should be performed using baseline correction so that the calculated pharmacokinetic parameters refer to the additional concentrations provided by the treatment. Administration of supra-therapeutic doses can be considered in bioequivalence studies of endogenous drugs, provided that the dose is well tolerated, so that the additional concentrations over baseline provided by the treatment may be reliably determined.*
>
> *If a separation in exposure following administration of different doses of a particular endogenous substance has not been previously established this should be demonstrated, either in a pilot study or as part of the pivotal bioequivalence study using different doses of the reference formulation, in order to ensure that the dose used for the bioequivalence comparison is sensitive to detect potential differences between formulations.*
>
> *The exact method for baseline correction should be pre-specified and justified in the study protocol. In general, the standard subtractive baseline correction method, meaning either subtraction of the mean of individual endogenous pre-dose concentrations or subtraction of the individual endogenous predose AUC, is preferred. In rare cases where substantial increases over baseline endogenous levels are seen, baseline correction may not be needed.*
>
> *In bioequivalence studies with endogenous substances, it cannot be directly assessed whether carryover has occurred, so extra care should be taken to ensure that the washout period is of an adequate duration.'*

The use of C-peptide correction is in principle reasonable owing to the lack of a specific assay.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 5 shows the studies relating to each pharmacodynamic topic.

The studies are the same Phase I studies that have been considered in regard to pharmacokinetics. The used the same euglycaemic clamp method with the same sampling times and data management, excepting that those studies in healthy volunteers ran for only 24 hours. The results across studies were as expected consistent and comparable.

Table 5: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*Aim of Study
Primary Pharmacology	Effect on glucodynamics in a euglycaemic clamp study	ABEA ABEM ABEI ABEE	PK and PD PK and PD PK and PD PK and PD
Secondary Pharmacology	Effect on C-peptide levels in healthy volunteers#	ABEA ABEM ABEI	PK PK PK
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	Not done	
	Effect of age	Not done	
Comparison of Lantus EU versu Lantus US	'Scientific Bridge' to support Phase III studies use of both sources of Lantus	ABEN	PK and PD
Population PD and PK-PD analyses	Healthy subjects	Not done	
	Target population	Not done	

* Indicates the primary aim of the study.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.
# C-peptide levels are presented graphically as Figures only.
None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

The Phase I studies were more successful as PD studies than as PK studies notwithstanding the duration of most studies (24 hours).

The Phase I studies adequately address the requirements of the adopted EU guideline EMEA/CHMP/BMWP/32775/2005 Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-Clinical And Clinical Issues - Guidance On Similar Medicinal Products Containing Recombinant Human Soluble Insulin, noting that the short duration of studies in healthy volunteers could not capture the full duration of action of insulin glargine and that the study in patients with T1DM did not capture the full duration of action of insulin glargine in a minority of subjects in each and/or both periods:

> *'The clinical activity of an insulin preparation is determined by its time-effect profile of hypoglycaemic response, which incorporates components of pharmacodynamics and pharmacokinetics. Pharmacodynamic data are of primary importance to demonstrate comparability of a similar rh-insulin. The double-blind, crossover hyperinsulinaemic euglycaemic clamp study is suitable for this characterisation. Data on comparability regarding glucose infusion rate and serum insulin*

> *concentrations should be made available. The choice of study population and study duration should be justified. Plasma glucose levels should be obtained as part of the PK study following subcutaneous administration.'*

Abasria has a PD profile equivalent to Lantus and this is shown directly by glucodynamic parameters and by the influence on C-peptide levels in healthy volunteers. The Lantus used was EU derived Lantus.

Dosage selection for the pivotal studies

Abasria is modelled as a biosimilar version of Lantus, and the nonclinical (preclinical) data supported comparability of Lantus and Abasria. Therefore, the Phase III Studies treated the enrolled patients according to the locally approved PI of Lantus and according to a reasonable treatment algorithm (Study ABEC) or reasonable principles (Study ABEB).

Efficacy

Studies providing efficacy data

Lantus is registered with the following composite indication, as represented in the PI:

> *'Insulin glargine is 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.'*

The first indication is subdivided in to adults and children; the second is limited to adults.

There are two Phase III studies in this submission, Study ABEC and Study ABEB.

Table 6: Brief description of the Phase III studies. Phase III Efficacy and Safety studies supporting the use of LY2963016 in patients with T1DM and T2DM

Type 1 Diabetes Mellitus	
Study ABEB	Phase 3, randomized, multinational, multicenter, 2-arm, active-control, open-label, parallel, 24-week treatment study with an ongoing 28-week active-controlled extension and 4-week post-treatment follow-up to compare LY2963016 and LANTUS® when each was used in combination with mealtime insulin lispro in adult patients with T1DM. All patients were started on 1:1 (unit-to-unit) conversion of prestudy basal/bolus insulins to study insulins (LY2963016 or LANTUS® as basal, lispro as mealtime bolus). Insulin adjustments were made to achieve or maintain glycemic goals (HbA1c <7.0%, FPG ≤6.0 mmol/L [108 mg/dL], other preprandial capillary BGs 70 to130 mg/dL [3.9 to 7.2 mmol/L], without incurring hypoglycemia). Patients administered their basal insulin using prefilled pen injectors. This study is ongoing; safety results from the 24-week treatment period are presented in this summary.
Type 2 Diabetes Mellitus	
Study ABEC	Phase 3, randomized, multinational, multicenter, 2-arm, active-control, double-blind, parallel, 24-week treatment study with a 4-week post-treatment follow-up to compare LY2963016 and LANTUS® when used in combination with at least 2 OAMs, in adult patients with T2DM. Patients entering on LANTUS® received LY2963016 or LANTUS®, based on randomization, at the same dose and timing as their prestudy LANTUS® by unit-to-unit conversion. Patients who were insulin naïve were started on 10 U once-daily of LY2963016 or LANTUS®, based on randomization. Patients were provided covered insulin vials, and administered their insulin using a syringe. Patient-driven titration included the addition of 1 U daily until a FBG ≤100 mg/dL (5.6 mmol/L) was achieved; in cases where patients had to use a syringe marked with 2 U increments, the patient-driven titration was modified to allow the addition of 2 U every other day until a FBG ≤100 mg/dL (5.6 mmol/L) was achieved.

Abbreviations: BG = blood glucose; FBG = fasting blood glucose; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; OAM = oral antihyperglycemic medication; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Evaluator's conclusions on efficacy

The first indication is subdivided in to adults and children; the second is limited to adults.

In regard to T1DM, Study ABEB satisfied the requirements of its a priori sample size calculations and analytical plan. It was conducted in the light of advice received from the FDA and from the EMA. The study groups were well matched. However, Study ABEB was of open label design and it is uncertain as to how much this might have affected the behaviour of investigators in order to achieve similar improvements in both groups against baseline glycated haemoglobin (HbA1c) readings. Within this major limitation, Study ABEB supports equi-efficaciousness of Abasria and Lantus as the basal insulin component in the treatment regimen of patients with T1DM. The supportive efficacy outcomes in Study ABEB are of doubtful clinical value.

In regard to Type 2 Diabetes Mellitus (T2DM), the evaluator accepts that comparable efficacy to Lantus EU and Lantus US was shown in Study ABEC, a study that exceeded the predetermined sample size and that had a modest dropout rate. The results of the study show comparable efficacy, including comparable improvement from baseline in both treatment groups that is comparable also in terms of subgroups of previous Lantus use or insulin-naïve patients. The patient population was reasonably representative of patients with T2DM who require basal insulin, matching Lantus' registered indication. It is clear that a large majority of subjects was not tightly controlled at study entry.

Safety

Studies providing safety data

The following types of studies provided evaluable safety data:

- Phase I Studies
- Phase III Studies

The Phase I Studies were numerically dominated by the use of healthy volunteers, so most adverse events were procedure related (invasive procedures, inter-current illnesses and hypoglycaemia). No new safety concerns arose from these Phase I studies.

The erratic absorption of insulin, in some individuals in at least one period of the replicate studies, suggests limits to the reliability of insulin glargine (whether as Abasria or Lantus) as a slow release pharmaceutical.

The Phase III Studies are of uneven quality (ABEC was blinded; ABEB was open) but both were large enough to define common adverse events and both included a blinded centralised review of possible immunological adverse events as well as binding activity of insulin antibodies.

The evaluator has referred to ABEB and ABEC as 'Phase III Studies' rather than 'pivotal' studies in this section because it was not considered that ABEB is a pivotal study.

Phase III efficacy studies

In the Phase III efficacy studies, the safety data were collected according to this tabulation:

Table 7: Study schedule. Protocol I14L-MC-ABEC

	Visit																	
Description of Event	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**801**	**ED**
Week of Study	-2	0	1	2	3	4	6	8	10	12	14	16	18	20	22	24	28	
Allowable Deviation +/- (days)	7	--	3	2	3	2	3	3	3	3	3	3	3	3	3	3	7	
Telephone Visit			x		x		x		x		x		x		x			
Screen Inclusion																		
Informed Consent Obtained	x																	
Patient Number Assigned	x																	
Randomization		x																
Diet/Exercise Counseling[a]		x																
Clinic Assessments																		
Medical History	x																	
Physical Exam	x																	
Height	x																	
Preexisting Conditions	x																	
Weight	x	x		x		x		x		x		x		x		x	x	x
Vital Signs (sitting) SBP, DBP, and HR	x	x		x		x		x		x		x		x		x	x	x
Lab Assessments[g]																		
Chemistry	x															x		x
Hematology	x															x		x
Pregnancy Screen[h]	x																	
ECG (local)	x																	
HbA1c	x	x				x		x		x		x		x		x		x
Insulin Antibodies		x				x				x						x	x[i]	x

Abbreviations: BG = blood glucose; Concom Meds = concomitant medications; DBP = diastolic blood pressure; DNA = deoxyribonucleic acid; eCRF = electronic case report form; ED = early discontinuation; ECG = electrocardiogram; HbA1c = hemoglobin A1c; HR = heart rate; pt = point; SBP = systolic blood pressure; SMBG = self-monitored blood glucose.

a Additional training should have been provided as needed throughout the study.
b Adverse events, hypoglycemic episodes, concomitant medications, and the last 3 available profiles of 4-point SMBG reported at telephone visits should have been recorded on the eCRF at the next office visit.
c Study sites retained study diaries.
d Patients should have performed three 7-point SMBG profiles during the 2-week period prior to these visits. The 7-points were before the morning, mid-day, and evening meals; 2 hours after the morning and midday meals; bedtime, and at 3 am.
e Transferred values from the study diary, if available.
f The 3 days of 4-point SMBG values used as a reference from the telephone visit were to be validated and entered into the eCRF from the source diaries. These values should have been within 1 week (or 2 weeks, if applicable) prior to the telephone visit preceding the office visit when data were transferred to eCRF. In certain instances (eg, between Visits 2 and 4), it may have been from the same days as those used for the 7-point SMBGs.
g Analyses should have been performed at a central laboratory unless otherwise noted and could have been repeated for cause in case of adverse events.
h A pregnancy test was to be performed on all females of childbearing potential at Visit 1, and when clinically indicated, and was to be performed locally. A serum or urine test was acceptable.
i 4-weeks post-endpoint, blood was to be collected for insulin antibody assay storage for future reference, if needed.
j Study sites retained questionnaires.
k This questionnaire should have been administered only if the patient had received at least 1 dose of study drug.

Phase III studies that assessed safety as a primary outcome

Neither Study ABEC nor Study ABEB had specific safety objectives as primary outcomes. It is noted that both had one secondary outcome that is arguably safety-related,

'*To compare LY2963016 relative to Lantus® with regard to intrapatient blood-glucose (BG) variability; basal and prandial (separately and as total daily) insulin dose; and weight when used in combination with pre-meal insulin lispro.' This outcome has been presented in the efficacy discussion of each study (See sections 21.7 and 22.4.1.3 of this report). Study ABEC had also this secondary outcome: 'To compare the safety of LY2963016 relative to Lantus® (eg, incidence of anti-insulin antibodies, hypoglycemia, adverse events [AEs]) when used in combination with OAMs*'.

Dose-response and non-pivotal efficacy studies

Not applicable.

Other studies evaluable for safety only

Not applicable.

Phase three studies that assessed safety as a primary outcome

Not applicable.

Patient exposure

Phase III studies

As noted in the sponsor's Safety summary, a total of 536 patients with T1DM and 759 patients with T2DM were randomly assigned to treatment in Studies ABEB and ABEC, respectively. Of these patients, a total of 535 patients with T1DM and 756 patients with T2DM received at least one dose of randomly assigned study drug, comprising the Full Analysis Sets (FAS) and serving as the populations of interest for analyses in the applicant's safety analyses. The mean duration of exposure for patients in Study ABEB was 23.32 weeks and 23.66 weeks for the Abasria and Lantus® groups, respectively; mean duration of exposure in Study ABEC was 22.38 and 22.13 weeks, respectively. The dose of insulin glargine was according to the same treatment paradigm in each study; the locally approved PI informed the use of insulin glargine.

The following comparative table is from sponsor's Safety Summary; it matches the patient numbers in the study reports.

Table 8: Exposure (by duration) to Abasria and Lantus in Phase III clinical studies.

	ABEB (T1DM)		ABEC (T2DM)	
	LY2963016 (N = 268)	LANTUS® (N = 267)	LY2963016 (N = 376)	LANTUS® (N = 380)
Exposure Duration (weeks)				
Mean (SD)	23.32 (3.74)	23.66 (2.95)	22.38 (5.37)	22.13 (5.75)
Exposed for:				
≥18 weeks, n (%)	257 (95.9)	260 (97.4)	338 (89.9)	334 (87.9)
≥24 weeks, n (%)	189 (70.5)	190 (71.2)	257 (68.4)	270 (71.1)

Abbreviations: N = total number of patients; n = number of patients in the specified category; SD = standard deviation; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
Sources: ABEB CSR (Table ABEB.12.1); ABEC CSR (Table ABEC.12.1).

There is no experience beyond the cut-off point of Studies ABEB and ABEC, that is, 24 weeks on treatment.

Safety issues with the potential for major regulatory impact

Neoplasms

A few neoplasms were reported in both studies. The matter deserves long term targeted surveillance because:

- Insulin glargine is agonistic at the Insulin-like Growth factor (IGF-1) receptor
- The approved PI of Lantus states,
  '*IGF-1 receptor binding: The affinity of insulin glargine for the human IGF-1 receptor is approximately 5 to 8-fold greater than that of human insulin (but approximately 70 to 80-fold lower than the one of IGF-1), whereas M1 and M2 bind the IGF-1 receptor with slightly lower affinity compared to human insulin. The total therapeutic insulin concentrations (insulin glargine and its metabolites) found in type 1 diabetic patients was markedly lower than what would be required for a half maximal occupation of the IGF-1 receptor and the subsequent activation of the mitogenic-proliferative pathway*

initiated by the IGF-1 receptor. Physiological concentrations of endogenous IGF-1 may activate the mitogenic proliferative pathway; however, the therapeutic concentrations found in insulin therapy, including in Lantus therapy, are considerably lower than the pharmacological concentrations required to activate the IGF-1 pathway.'

- The above might not always apply for example, when early release of insulin glargine occurs from the site of injection, as happened in the Phase I studies. A non-selective assay was used but it is likely that insulin glargine, not M1 was released. Consequently, intermittent release of insulin glargine from the site of injection, in a setting of long term use, has not been excluded.
- The matter has been discussed in the literature since the publication of a retrospective cohort study of German health insurance fund records.[9] A dose-dependent increase in cancer risk was found for treatment with insulin glargine compared with human insulin. The matter has been kept under review by the EMA. The most recent statement was published on 31 May 2013 (EMA/329790/2013 EMEA/H/C/000309). The statement commenced with,

  > *'On 30 May 2013, the European Medicines Agency completed a review of new data on the cancer risk with insulin glargine-containing medicines. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the data do not show an increased risk of cancer and that the balance of the medicine's benefits and risks remains unchanged.'*

  New information was derived from two further cohort studies and from a case-control study.

  > *'Based on the assessment of the population-based studies, the CHMP concluded that overall the data did not indicate an increased risk of cancer with insulin glargine, noting that there is no known mechanism by which the insulin glargine would cause cancer and that a cancer risk has not been seen in laboratory studies. As for all medicines, the Agency will continue to assess any new data that become available in this area, as part of the routine monitoring of the medicine.'*

- There is difference between '*no known mechanism by which the insulin glargine would cause cancer*' (there is no suggestion that insulin glargine is for example genotoxic) and a potential to promote tumours by an agonistic effect at IGF-1 receptors. Consequently, postmarketing surveillance will possibly be contributory but the studies would need to be long term and be capable of dealing with confounders such as HMG CoA reductase inhibitors and low dose aspirin, both of which are commonly prescribed to diabetic patients.
- Nonetheless, there is no basis for suggesting that Abasria presents a different degree of risk from Lantus, so registration of Abasria cannot be opposed on the grounds of potential neoplasia.

Postmarketing data

At the time the TGA assessed this application, marketing had not yet occurred in any country.

[9]Hemkens LG, Grouven U, Bender R, Günster C, Gutschmidt S, Selke GW, Sawicki PT. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia 009; 52:1732–1744.

Evaluator's conclusions on safety

The Phase III studies are of sufficient size and duration to establish in terms of common adverse events. They enrolled reasonably representative populations of Type 1 and Type 2 diabetics that were using treatment regimens relevant to recommended clinical practice in this country. The study in Type 1 diabetics has an ongoing extension phase that should be submitted as a postregistration commitment. Its open design admits the possibility of bias.

No new safety signals emerged and Abasria was not worse than Lantus in terms of the frequency of serious adverse events. Abasria appears to be registrable on clinical safety grounds. The 12 month data on Study ABEB should be submitted for evaluation when they become available.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Abasria in the proposed usage are:

- Not different from those of Lantus EU and Lantus US based on two way non-inferiority in two Phase III studies.

First round assessment of risks

The risks of Abasria in the proposed usage are:

- Not different from those of Lantus EU and Lantus US based on the experience in two Phase III studies.
- There is an unresolved potential problem about the safety in use of the cartridge in an unspecified pen injector device (possibly HumaPen). There is in addition an unresolved issue concerning clinical data to support the KwikPen device. No data are able to be located by the evaluator to address these concerns.

First round assessment of benefit-risk balance

The benefit-risk balance of Abasria cartridges is unfavourable given the proposed usage, but would become favourable if the uncertainty raised should be resolved.

First round recommendation regarding authorisation

Registration should not proceed at present, pending resolution of the matters raised.

Submission of the completed (52 weeks of data) Study ABEB should be a condition of registration.

Clinical questions

Pharmacokinetics

1. In Study ABEN, the source of the US Lantus in unclear. The applicant should confirm and clarify how this can be correct.
2. The applicant should clarify who was the investigator and whose signature appears on I4L-MC-ABEI CSR Appendix Signature. The applicant should also confirm that Lantus EU was used in Study ABEI.

Second round evaluation of clinical data submitted in response to questions

The sponsor responded to the issues raised about the KwikPen as follows:

'There is no basis for the assumption that medication error is more likely to occur with Abasria compared to other insulins currently available, including the reference product in this application, without a dedicated pen and should therefore be removed from the evaluation report. The evaluator also states no information is available on the KwikPen device with respect to dose accuracy. This statement is incorrect as Module 3.2R.3 includes the required device testing information.'

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU Risk Management Plan Version 1.0 (dated 22 May 2013, Data-lock point 01 April 2013) and Australian Specific Annex Version 2 (dated 21 May 2014) which was reviewed by the TGA's Post-Market Surveillance Branch (PMSB).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 9.

Table 9: Ongoing safety concerns provided by the sponsor in their RMP submission.

Summary of Safety Concerns	
Important Identified Risks	• Hypoglycaemia • Hypersensitivity reactions • Medication errors (incorrect insulin) • Interaction with TZD
Important Potential Risks	• Neoplasms • Antigenicity
Important Missing Information	• Use in pregnancy • Use in children less than 2 years of age

Abbreviations: TZD = thiazolidinedione.

Pharmacovigilance plan

The sponsor proposes only routine pharmacovigilance activities for all ongoing safety concerns.

Risk minimisation activities

The sponsor proposes only routine risk minimisation activities for all ongoing safety concerns.

Reconciliation of issues outlined in the RMP report

Table 10 summarises the PMSB's first round evaluation of the RMP, the sponsor's responses to issues raised by the PMSB and the PSMB's evaluation of the sponsor's responses.'

Table 10: Reconciliation of issues outlined in the RMP evaluation report (Round 1)

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	PSMB evaluator's comment
1.1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.	*'The questions received did not require an amendment to the Risk Management Plan (RMP).'*	
1.2. The sponsor is advised to revise the ASA document.	*'The sponsor has revised the Australian Specific Annex document according to the guidance received.'*	
1.3. The sponsor should add these Ongoing Safety Concerns to the risk management plan: Cardiovascular events; Lipodystrophy; and Oedema.	*'Cardiovascular (CV) events* *The sponsor believes that the data from the ORIGIN study precludes the need for adding CV events (The ORIGIN Trial Investigators, 2012). Cardiovascular events will be part of routine pharamacovigilance monitoring and automated signal detection would ensure any untoward increase in frequency or severity would be noted and evaluated.* *Lipodystrophy* *Lipodystrophy is a risk for Abasria; however, it does not rise to the level of important as defined in Good Pharmacovigilance Practice) Module V (Rev 1). This risk does not have an impact on the benefit-risk balance of the product or have implications for public health and thus should not be included in the RMP.*	This is considered acceptable in the context of this application. However, the EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems also states that Important Identified Risks include conditions which can substantially affect a person's quality of life.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	PSMB evaluator's comment
	Oedema *Oedma based on insulin-related sodium retention is identified in the PI within the adverse event (AE) table as a recognised event; however, it does not rise to the level of an important identified risk. Oedema in conjunction with thioazolidinedione is already included as a safety concern, as it appears to be a more severe outcome for this drug-drug interaction.'*	
1.4. Unless the sponsor can provide a compelling justification, children below 18 years of age should be added as important missing information and a relevant and appropriate PI change should be made.	*'The sponsor believes that children younger than 18 years have been adequately studied by the innovator product and are included in the approved indications in the US (age 6 and older), EU (age 2 and older) and in Australia (age 2 and older). The use of insulin glargine for the treatment of T1DM in a pediatric population was originally supported by data establishing the safety and effectiveness of subcutaneous injections of insulin glargine (Lantus®) in patients aged 6 years and older.[10] The data for children between 2 and 6 years of age (the PRESCHOOL study) was recently published and shows clinical outcomes in children similar to those of adults.[11] Assessments of plasma 'trough' levels of insulin glargine revealed plasma concentration patterns similar to adults. Assuming the TGA, upon review of the marketing authorisation application concludes that Abasria is biosimilar to Lantus®, that conclusion should carry over to the pediatric population as well*	This is considered acceptable in the context of this application, if the Delegate has no objections to accept the Lantus data for ABRASIA.

[10] Schober, E, Schoenle E, Van Dyk J and Wernicke-Panten K, Comparative Trial Between Insulin Glargine and NPH Insulin in Children and Adolescents With Type 1 Diabetes. Letters Diabetes Care, Volume 24, Number 11, 2005 November 2001

[11] Danne T, Philotheou A, Goldman D, Guo X, Ping L, Cali A, Johnston P. A randomized trial comparing the rate of hypoglycemia-assessed using continuous glucose monitoring-in 125 preschool children with Type 1 diabetes treated with insulin glargine or NPH insulin (the PRESCHOOL study). *Pediatric Diabetes.* 2013;14(8):593-601.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	PSMB evaluator's comment
	for the purpose of labeling. *The sponsor agrees that adequate data are not available for children younger than 2 years and will include this age category as important missing data in the RMP.'*	
1.5. The sponsor should conduct a study (or assign an existing study) to investigate the potential risk of malignancies further, in particular in children.	*'The initial concern over the relationship of insulin glargine and malignancy was raised in 2009 in a published Pharmacoepidemiology survey. Sanofi-Aventis, the Lantus® sponsor, conducted 3 additional surveys, covering a total of almost 2 million patient lives, to explore this question, with conflicting results. In addition, Sanofi altered the secondary endpoints of the ORIGIN study, a 12,000-patient, prospective, 6 year longitudinal study in prediabetic and diabetic patients to explore the incidence of malignancy and also conducted a prospective study in patients with breast cancer who were newly diagnosed as diabetic and were insulin naïve. This study was planned after Committee for Medicinal Products for Human Use (CHMP) concluded that the other potential risks of a causal relationship between the use of insulin analogues and malignancy had apparently been discharged. The CHMP report from 31 May 2013 concluded 'that overall the data did not indicate an increased risk of cancer with insulin glargine, noting that there is no known mechanism by which the insulin glargine would cause cancer and that a cancer risk has not been seen in laboratory studies.'* *Neither the initial report nor any subsequent reports have reported an increased risk of malignancy in children using insulin analogues. The paediatric diabetic population is increasing in prevalence but remains small, and*	This is not considered acceptable. The OPR evaluator acknowledges that the reported incidence of malignancy is low and that a paediatric diabetic population is receiving more medical monitoring. However, considering that many paediatric malignancies may be discovered late, that medical monitoring for diabetes would not necessarily increase the probability of detecting a malignancy, and that insulin glargine is a widely used medicine, the sponsor should conduct a study (or assign an existing study) to investigate the potential risk of malignancies in children further. This recommendation remains.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	PSMB evaluator's comment
	the number of diabetic children who either have or are likely to develop a malignancy is also quite small. To collect the number of subjects needed to reach a conclusion with any degree of reliability would require several decades of enrolment in a prospective clinical trial or an epidemiology survey to collect sufficient sample size to be able to reach reliable conclusions or the availability of many hundreds of thousands of children with exposure to insulin analogues. *Accordingly, the sponsor believes that the demonstration of biosimilarity in the adult population should extend biosimilarity to the pediatric population on the basis of the innovator's paediatric data, and furthermore, the ability to conduct any epidemiologic survey or prospective study would require a prolonged period to accumulate the population exposure required for a statistically valid analysis. In the entire 14-year period since the innovator product first became available, there has been no signal suggesting a malignancy risk in the paediatric population. On this basis, the sponsor would decline acting on the recommendation.'*	
1.6. The sponsor recognises that this product is indicated for patients that are 2 years of age or older. This is not reflected in the proposed PI, as the PI refers to an age of 6 years and older. The sponsor is advised to remove this inconsistency. Furthermore, unless the sponsor has a compelling justification, children below the age of 18 years of age constitute important missing information which needs to be reflected in the PI.	*'The sponsor has corrected the inconsistency. This product is indicated for patients that are 2 years of age and older.* *Regarding the important missing information statement in the PI, the sponsor agrees that there are inadequate data on children younger than 2 years of age and will include that statement in the RMP. The rationale for this response is provided in the response to Recommendation 1.4.'*	This is considered acceptable in the context of this application. This is qualified in the comment in response to recommendation 1.4.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	PSMB evaluator's comment
1.7. In the 'Precautions' section, under the 'Hepatic Impairment' heading, the sponsor should include a statement that use in patients with rapidly deteriorating hepatic function is not recommended and the increased risk of hypoglycaemia in these patients (or a statement to that effect).	*'The sponsor believes that a biosimilar and the innovator product should present the same information and declines acting on the recommendation.'*	The reason given by the sponsor is not sufficient to warrant non-inclusion. Each submission is assessed individually. The recommendation to the Delegate remains.
1.8. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to accommodate the changes made to the product information document.	*'The sponsor has revised the draft CMI and provided it in Module 1.3.2.'*	This is considered acceptable.
1.9. In the 'How to use Abasria' section, the PI should contain a statement regarding the compatibility of the supplied cartridge with other insulin pens (if any) (or a statement to that effect).	*'The requested information is already provided in the 'preparing a dose' section and this does not need to be duplicated.'*	This is considered acceptable.

Summary of recommendations

It is considered that the sponsor's response to the TGA request for further information has adequately addressed most of the issues identified in the RMP evaluation report (other than PI recommendations).

Outstanding issues

It is considered that the sponsor's response to the TGA request for further information has adequately addressed most the issues identified in the RMP evaluation report (other than PI recommendations).

Summary of outstanding issues (including additional recommendations)

The sponsor should conduct a study (or assign an existing study) to investigate the potential risk of malignancies further, in particular in children.

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised.

Advice from Advisory Committee on the Safety of Medicines (ACSOM) has been sought at the request of the Delegate.

Key changes to the updated RMP

- EU Risk Management Plan Version 1.0 (dated 22 May 2013, Data Lock Point (DLP) 01 April 2013) and Australian Specific Annex Version (no version given, undated)

has been superseded by:

- EU Risk Management Plan Version 1.0 (dated 22 May 2013, Data Lock Point (DLP) 01 April2013) and Australian Specific Annex Version 2 (dated 21 May 2014).

It is noted that in the Australian Specific Annex Version 2 (dated 21 May 2014), the sponsor seems to refer to an EU Risk Management Plan Version 2.0. However, after consulting with the sponsor, it was found that the updated ASA also refers to EU Risk Management Plan Version 1.0.

Table 11: Key changes to the ASA

Summary of key changes between Australian Specific Annex (no version given, undated) and Australian Specific Annex Version 2 (dated 21 May 2014)	
Safety specification	Part II:SI, SII, SIII, SVII added
Pharmacovigilance activities	Part III: III.1 added Updated Table V.1 Use in children to reflect changes in the reference label; from less than 6 years to less than 2 years

Suggested wording for conditions of registration

Any changes to the RMP that were agreed to by the sponsor become part of the RMP, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise. The suggested wording is:

- Implement EU Risk Management Plan Version 1.0 (dated 22/05/2013, DLP 01/04/2013) and Australian Specific Annex Version 2 (dated 21/05/2014), and any future updates (where TGA approved) as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Abasria has the same pharmaceutical form and strength as the reference product, Lantus.

The primary amino acid sequence of the active ingredient for Abasria is the same as that for Lantus.

Each mL of Abasria contains: 100 units of insulin glargine, zinc oxide, metacresol, glycerol and water for injections; as well as hydrochloric acid and sodium hydroxide for pH adjustment.

There are some differences in excipients: zinc oxide replaces zinc chloride, 100% glycerol replaces 85% glycerol.

The biosimilar comparability testing included structural characterisation, physicochemical characterisation, biological potency, impurity characterisation and stability assessment. Impurities were low and adequately controlled.

The biological chemistry evaluator concluded that comparability between Abasria and EU approved Lantus has been satisfactorily established.

The biological chemistry evaluator accepted the sponsor's justification for use of the EU sourced Lantus for Australian registration.

Nonclinical

The nonclinical evaluator had no objections to registration. The scope of the nonclinical program complied with the relevant EU guideline.

Comparability was shown between Abasria and EU sourced Lantus (and depending on the study, US sourced Lantus) on:

- pharmacological activity (receptor binding affinity and functional activity in cell-based assays; glucodynamic profile in vivo in rats);
- toxicity profile (assessed in 4 week, GLP compliant studies in rats).

Clinical

Pharmacokinetic and pharmacodynamic studies

For a biosimilar insulin, the draft Committee for Medicinal Products for Human Use (CHMP) guidance12, 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 III 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 III 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 III studies is to establish safety [and exclude any reduction in efficacy]; by measuring immunogenicity endpoints.)

The CHMP agreed with the sponsor that studies in healthy volunteers provide a more homogeneous and sensitive PK comparability model than studies in patients with diabetes. Consequently, all PK/PD studies were done in healthy volunteers; except of ABEE, which was done in patients with T1DM.

PK studies used C-peptide-corrected insulin concentration-time data. Given the flat time-concentration profile, AUC is the most sensitive measure; C_{max} is less sensitive.

For the PD measurements, the draft CHMP guideline[12] states that the euglycaemic clamp technique is the best available method for measurement of insulin action. In these clamp studies, the plasma insulin concentration is raised (by subcutaneous injection of insulin) and the blood-glucose level maintained ('clamped') at a pre-defined level by means of variable infusion of glucose. The main variable of interest is the time profile for the glucose infusion rate: AUC and C_{max}; denoted G_{tot} and R_{max}, below.

[12] EMEA/CHMP/BMWP/32775/2005_Rev.2

Table 12: PK/PD studies

Study	Comparison	n (planned)
ABEA	Abasria versus EU-approved Lantus (pivotal)	80
ABEI	Abasria versus EU-approved Lantus (pilot)	16
ABEM	Abasria versus EU-approved Lantus (2 doses)	24
ABEE	Abasria versus EU-approved Lantus (T1D)	20
ABEN	EU-approved Lantus versus US-approved Lantus (Abasria not studied)	40
ABEO	PK/PD similarity of Abasria and EU-approved Lantus [no completed at time of submission; to support the application to the FDA]	91

Table 13: Results for pivotal ABEA study, healthy volunteers, ratio of least squares geometric means, dose=0.5 U/kg, completers

PK parameters		PD parameters	
$AUC_{[0-24]}$ pmol.hr/L n Point estimate (90% CI)	C_{max} pmol/L n Point estimate (90% CI)	G_{tot} mg/Kg n Point estimate [95% CI]	R_{max} 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]

Gtot (total amount of glucose infused during the euglycaemic clamp procedure). Rmax (maximum glucose infusion rate)

Summary of other PK/PD studies

- ABEI (n=16); this pilot assessed the relative bioavailability and PD response of Abasria versus EU approved Lantus. This was a single-dose (0.5 U/kg), open label study in normal-weight healthy volunteers; insulin levels were corrected for baseline C-peptide level; results were supportive; point estimates for insulin (AUC, C_{max}) and glucose infusion (G_{tot}, R_{max}) were indicative of biosimilarity. Some of the 90% confidence limits did not meet the 80%-125% acceptance limits but this is not surprising, given the small sample size.
- ABEM (n=24) assessed the relative bioavailability and PD response of Abasria versus EU approved Lantus at two single doses: 0.3 U/kg and 0.6 U/kg. At both doses, results were supportive.
- ABEE (n=20) assessed the duration of action of Abasria versus EU approved Lantus (0.3 U/kg) in patients with T1D (mean age=42 years) (all the other studies were in healthy volunteers). These were stable T1D patients who were receiving baseline insulin treatment. The study was primarily PD in nature and its main objective was to compare the duration of action of Abasria and EU sourced Lantus. The median duration of action was estimated to be 37.1 and 40.0 hours for Abasria and Lantus, respectively. A survival analysis was carried out with a Cox PH model; Hazard ratio (HR)=1.063, p=0.8777; supporting the conclusion that there does not seem to be a significant difference in duration of action between Abasria and Lantus.

· ABEN (n=40; 34 completers) showed similarity of EU sourced and US-sourced Lantus.

Table 14: PK results from Study ABEN

PK parameters		PD parameters	
$AUC_{[0-24]}$ pmol.hr/L n Point estimate (90% CI)	C_{max} pmol/L n Point estimate (90% CI)	G_{tot} mg/Kg n Point estimate [95% CI]	R_{max} mg/Kg n Point estimate [95% CI]
n=32 0.97 (0.89, 1.04)	n=34 0.97 (0.90, 1.04)	n=34 1.02 [0.88, 1.19]	n=34 0.98 [0.87, 1.11]

· ABEO (n=91) was requested by the FDA (Abasria versus US sourced Lantus). Results were not available at the time the dossier was submitted.

Phase III studies

The primary focus of the two Phase III studies (ABEB, ABEC) was the evaluation of immunogenicity and implications this might have for safety (or any reduction in efficacy). The EMA advised the sponsor that formal demonstration of non-inferiority in terms of antibody response was not required.

The EMA considered that HbA1c is not a sensitive enough endpoint on which to establish similar efficacy. For the purposes of establishing efficacy, the results for HbA1c were considered supportive to the PK/PD studies.

Both studies were multinational (ABEB: 59 centres in 9 countries; ABEC: 88 centres in 13 countries). Patients in the comparison group either received EU-approved Lantus or US approved Lantus depending on the site (EU approved Lantus: EU, Mexico, Japan, South Korea, Taiwan; US approved Lantus: US, Puerto Rico). The sponsor argued that given the scientific bridge demonstrated in the PK/PD studies, it was not necessary to stratify the results by EU-Lantus versus US-Lantus.

Table 15: Characteristics of studies ABEB and ABEC

	ABEB, n=535	ABEC, n=756
T1/T2	T1DM	T2DM
Time period	September 2011- August 2012	September 2011-September 2012
Time horizon	24 week; 28 week extension	24 week
Blinding	Open-label	Blinded
Dose regimen	Starting dose was same dose as patient's pre-study basal insulin	Starting dose was same dose as patient's pre-study basal insulin; or if insulin naive: 10 U QD
Inclusion criteria	men and women 18+ years BMI<35 kg/m^2 HbA1c<11% On basal-bolus insulin>1 year That is, well-controlled T1D patients managed on Lantus, NPH insulin or insulin detemir	men and women 18+ years BMI<45 kg/m^2 HbA1c: 7%-11%, if insulin naïve HbA1c<11% if pre-study Lantus 2+ oral anti-diabetic medications That is, well-controlled T2D patients managed on 2+ oral anti-diabetic medications and who were either insulin naïve or treated with Lantus

Table 16: Baseline characteristics

	ABEB (T1DM) n=535		ABEC (T2DM) n=756	
	Abasria n=268	Lantus n=267	Abasria n=376	Lantus n=380
Age (years) Mean Min, Max	 41 18, 81	 41 20, 72	 59 23, 84	 59 27, 82
Men (%)	58%	58%	48%	52%
Duration of diabetes (years) Mean Min, Max	 16 1, 54	 17 1,55	 12 0.5, 40	 11 0.4, 34
BMI (kg/m^2) Mean Min, Max	 26 17, 38	 25 19, 36	 32 20, 46	 32 20, 46
HbA1c (%) Mean Min, Max	 7.8 4.8, 11.5	 7.8 5.2, 10.3	 8.3 4.9, 11.3	 8.3 5.9, 11.2
Entry basal insulin (%) Lantus None Other	 81 0 19	 88 0 12	 41 59 0	 38 62 0

Insulin antibodies

The proportions of patients with detectable antibodies and treatment-emergent antibody response (TEAR) were reported.

Definition of TEAR: 1+% increase (absolute) in insulin antibody levels (measured in percent binding) and a 30+% relative increase from baseline for patients who were insulin antibody-positive at baseline, or changed from insulin antibody-negative status at baseline to antibody-positive during the course of the study.

The proportions of patients with detectable antibodies were similar for Abasria and Lantus in both ABEB and ABEC.

Table 17: 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	
	Abasria N=265 n (%)	Lantus N=267 n (%)	Abasria 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)[a]	79 (30)	90 (34)	56 (15)	40 (11)

a) overall (anytime) during treatment period, not including baseline

For ABEB, at 52 weeks, the proportion of patients with detectable antibodies was similar. For example, for overall (anytime) the proportions were: Abasria (38%) versus Lantus (39%).

Stratified analyses by TEAR did not show any differences for Abasria versus Lantus by HbA1c, basal insulin dose, or hypoglycaemia.

Table 18: Relationship between overall TEAR status and clinical outcomes. Change from baseline to week-24

	ABEB (T1DM) N=535		ABEC (T2DM) N=756	
	Abasria N=265 n (%)	Lantus N=267 n (%)	Abasria N=365 n (%)	Lantus N=365 n (%)
HbA1c (%)				
TEAR				
Number of patients	56	52	45	34
LS change	-0.24	-0.48	-1.26	-1.49
No TEAR				
Number of patients	209	215	320	331
LS change	-0.37	-0.44	-1.27	-1.31
Basal insulin dose (U/day)				
TEAR				
Number of patients	56	52	45	34
LS change	1.19	2.04	34.66	35.99
No TEAR				
Number of patients	209	215	320	331
LS change	2.30	2.04	31.85	31.95
Hypogylcaemia (episodes/30-days)				
TEAR				
Number of patients	56	52	45	34
LS change	-1.16	-0.93	0.40	1.22
No TEAR				
Number of patients	209	215	320	331
LS change	-1.94	-2.53	0.62	0.96

Hypoglycaemia

Not surprisingly, the rate of hypoglycaemic attacks was greater in Study ABEB (T1D, all patients were insulin dependent at study entry) than study ABEC (T2D, approximately 60% of patients insulin-naïve at study entry).

There were no clinically meaningful differences in total, severe or nocturnal hypoglycaemia for Abasria versus Lantus (or relative or symptomatic or other categories hypoglycaemia, not included in the above summary table).

Table 19: Incidence of hypoglycaemia to 24 weeks

	ABEB (T1DM) n=535		ABEC (T2DM) n=756	
	Abasria n=268	Lantus n=267	Abasria n=376	Lantus n=380
Total hypoglycaemia Patients n (%) Events	252 (94%) 10404	254 (95%) 10985	296 (79%) 3564	292 (78%) 3845
Severe hypoglycaemia Patients n (%) Events	4 (1.5%) 6	8 (3.0%) 9	2 (0.5%) 7	2 (0.5%) 2
Nocturnal hypoglycaemia Patients n (%) Events	222 (83%) 2301	216 (81%) 2347	212 (57%) 1248	203 (54%) 1386

A hypoglycaemic event was defined as: any time a patient felt that he/she was experiencing a symptom or sign associated with hypoglycaemia or blood glucose ≤3.9 mmol/L (≤70 mg/dL).

Severe hypoglycemia was defined as a hypoglycemic event that required assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions. These episodes may have been associated with sufficient neuroglycopenia to induce seizure or coma. Blood glucose measurements may not have been available during such an event, but neurological recovery attributable to the restoration of BG to normal was considered sufficient evidence that the event was induced by low plasma glucose. Nocturnal hypoglycemia was defined as any hypoglycemic event that occurred between bedtime and waking.

The 52 week report for ABEB also did not show any clinically meaningful differences in hypoglycaemia.

Other safety data

There were no imbalances in serious adverse events or deaths.

There were no differences in treatment-emergent allergic events (for example, arthralgia, pruritus, rash, asthma and injection-site reactions). The majority of these events were mild and none led to discontinuation.

Efficacy from Phase III studies

Table 20: Results for HbA1c, 24 weeks

	ABEB (T1DM) n=535		ABEC (T2DM) n=756	
Full analysis set				
HbA1c (%)	Abasria n=268	Lantus n=267	Abasria n=376	Lantus n=380
Least squares mean change from baseline (LOCF)	-0.350	-0.456	-1.286	-1.338
Difference, point estimate (LOCF)	0.106		0.052	
Difference, 95% CI (LOCF)	(-0.005, 0.217)		(-0.070, 0.175)	
Per protocol analysis set				
HbA1c (%)	Abasria n=251	Lantus n=256	Abasria n=314	Lantus n=308
Least squares mean change from	-0.370	-0.468	-1.286	-1.338

	ABEB (T1DM) n=535		ABEC (T2DM) n=756	
baseline (LOCF)				
Difference, point estimate (LOCF)	0.098		0.116	
Difference, 95% CI (LOCF)	(-0.014, 0.209)		(-0.010, 0.242)	

These results meet the non-inferiority margin of 0.3% at 24 weeks for the endpoint of 'change in HbA1c'; although the point estimates show that Abasria was slightly worse than Lantus, in terms of HbA1c.

The updated analysis at 52 weeks for ABEB (T1D) also met the non-inferiority margin of 0.3%. For example, for the full analysis set, last observation carried forward (LOCF), Abasria -0.256%, Lantus -0.276%, least squares (LS) mean difference: 0.020%, (95% confidence interval (CI): 0.099%, 0.140%).

Results for secondary efficacy endpoints (such as fasting blood glucose and insulin dose) were consistent with those for HbA1c.

Risk management plan

No new risks were identified for Abasria and the risk management plan is based on that for Lantus. Important identified risks for Abasria/Lantus include hypoglycaemia, hypersensitivity reactions, injection site reactions, medication errors. Important potential risks include malignancies and immunogenicity. The plan is to mitigate these risks through routine risk minimisation measures (for example, education for prescribers through the PI and spontaneous reporting of adverse events).

Risk-benefit analysis

Delegate's considerations

The sponsor's clinical development program was conducted according to EMA guidelines and after discussion with EMA.

The PK/PD profiles of Abasria and Lantus are similar. Two Phase III studies have shown that the immunogenicity profiles of Abasria and Lantus are similar.

Establishment of non-inferior (similar) efficacy was not the primary aim of the Phase III studies (that is, the primary aim was to show that the immunogenicity profiles were similar). Point estimates for change in HbA1c were similar but slightly in favour of Lantus. (The 95% CI did not include the non-inferiority margin of 0.3%). These results are broadly supportive of the PK/PD data, which are the primary data that establish similar efficacy.

If the TGA's Advisory Committee on Prescription Medicines (ACPM) is satisfied that the submitted data show that Abasria is similar to Lantus, then the efficacy and safety of Abasria can be inferred from the evidence base for Lantus.

Conditions of registration

Implement EU Risk Management Plan Version 1.0 (dated 22 May 2013, Data Lock Point (DLP) 01 April 2013) and Australian Specific Annex Version 2 (dated 21 May 2014), and any future updates (where TGA approved) as a condition of registration.

The Australian Biological Name of the reference product may be used as the non-proprietary name of Abasria, however it is a condition of registration that when the International Nonproprietary Names (INN) Biological Qualifier proposal is adopted by the

World Health Organization, that the biosimilar identifier is used in all references to the product in the labelling, PI and CMI. When this change is made, the TGA should be informed and the labels, PI and CMI submitted for assessment and updating of the website.

Proposed action

The Delegate had no reason to say, at this time, that the application for Abasria should not be approved for registration.

Request for ACPM advice

- Does the ACPM consider that the PK/PD studies provide sufficient evidence to establish that Abasria has a PK/PD profile similar to that of Lantus?
- Does the ACPM consider that the Phase III studies provide sufficient evidence to establish that immunogenicity is similar to Lantus?
- Studies of similarity between Abasria and Lantus have been conducted in adults. Does the ACPM consider that these allow extrapolation of the similarity to children, 2 years and older?
- Biosimilars are not regarded as interchangeable on a same-dose basis with the reference product. That is, any switch from Lantus to Abasria should only be done under medical supervision and may require different dosing and particular caution regarding hypogylcaemia. Does the ACPM consider that the information provided in the PI is appropriate?

Response from sponsor

The sponsor's response will focus on the key areas of:

1. Paediatric population;
2. Interchangeability; and
3. Other matters for clarification for the benefit of committee deliberations.

1. Paediatric Population

The sponsor of the reference product Lantus® has conducted studies in children aged 2 years and older. The Australian package insert (PI) for Lantus contains the following statement regarding use in paediatric patients:

> *In general the safety profile for patients ≤18 years of age is similar to the safety profile for patients >18 years.*

Based upon the accepted similar safety of insulin glargine in adults and paediatric patients, the extensive postmarketing experience of the reference product in both populations, and the demonstrated comparability of Abasria to Lantus®, the sponsor concludes that Abasria is appropriate for use in the paediatric setting.

The Abasria PI proposes the following information for paediatric use consistent with the reference PI:

> *In general, the safety profile for patients ≤18 years of age is similar to the safety profile for patients >18 years. The adverse events reports received from Post Marketing Surveillance included relatively more frequent injection site reactions (injection site pain, injection site reaction) and skin reactions (rash, urticarial) in patients ≤18 years of age than in patients >18 years.*

> *Data from pooled clinical trials in adults and children aged 6 to 18 years did not show a greater incidence of either injection site reaction or skin reactions in the paediatric population compared to adults.*
>
> *Pharmacokinetics in children aged 2 to less than 6 years of age with Type 1 diabetes mellitus was assessed in one clinical study. Plasma 'trough' levels of insulin glargine and its main metabolites M1 and M2 were measured in children treated with insulin glargine, revealing plasma concentration patterns similar to adults, and providing no evidence for accumulation of insulin glargine or its metabolites with chronic dosing.*

The practice of adopting the reference product label following demonstration of comparability is consistent with the approach agreed to by the EMA and the FDA.

According to EU regulations, paediatric investigation has been waived for Abasria because the safety and efficacy of the reference product (Lantus) has been investigated in the paediatric population. Data on Lantus in paediatric populations have been published.[13] The EMA approved Abasria on 9 September 2014, including the Abasria Summary of Product Characteristics (SmPC) text based on the Lantus® SmPC shown below.

Lantus® SmPC Section 5.1 states:

> *Safety and efficacy of Lantus® (insulin glargine, Sanofi-Aventis) have been established in adolescents and children aged 2 years and older. Safety and efficacy of Lantus® have not been established in children below the age of 2 years.*

Lantus® SmPC Section 4.8 (Undesirable Effects) includes the following safety summary:

> *In general, the safety profile for children and adolescents (≤18 years of age) is similar to the safety profile for adults. The adverse reaction reports received from postmarketing surveillance included relatively more frequent injection site reactions (injection site pain, injection site reaction) and skin reactions (rash, urticaria) in children and adolescents (≤18 years of age) than in adults. Clinical study safety data are not available for children under 2 years.*
>
> *Additionally, the USPI will contain similar statements for paediatrics based on the findings of the reference product. The following is tentatively approved in the US PI (Note: The tradename for Abasria in the US is proposed as BASAGLAR):*
>
> *The safety and effectiveness of BASAGLAR have been established in pediatric patients (age 6 to 15 years) with Type 1 diabetes based on an adequate and well-controlled trial of another insulin glargine product in pediatric patients (age 6 to 15 years) with Type 1 diabetes and additional data in adults with type 1 diabetes. [see Clinical Studies (14.2)]. The safety and effectiveness of BASAGLAR in pediatric patients younger than 6 years of age with Type 1 diabetes and pediatric patients with Type 2 diabetes has not been established.*

[13] Schober E, Schoenie E, Van Dyk J, Wernicke-Panten K, Pediatric Study Group of Insulin Glargine. Comparative trial between insulin glargine and NPH insulin in children and adolescents with Type 1 diabetes mellitus. *J Pediatr Endocrinol Metab*. 2002;15(4):369-376.

Alemzadeh R, Berhe T, Wyatt DT. Flexible insulin therapy with glargine insulin improved glycemic control and reduced severe hypoglycemia among preschool-aged children with Type 1 diabetes mellitus. *Pediatrics*. 2005;115(5):1320-1324.

Danne T, Philotheou A, Goldman D, Guo X, Ping L, Cali A, Johnston P. A randomized trial comparing the rate of hypoglycemia-assessed using continuous glucose monitoring-in 125 preschool children with Type 1 diabetes treated with insulin glargine or NPH insulin (the PRESCHOOL study). *Pediatric Diabetes.* 2013;14(8):593-601.

NCT00993473 resource page. ClinicalTrials.gov web site. Available at http://clinicaltrials.gov/ct2/show/NCT00993473. Accessed September 10, 2014.

> *The dosage recommendation when changing to BASAGLAR in pediatric patients (age 6 to 15 years) with Type 1 diabetes is the same as that described for adults [see Dosage and Administration (2.2, 2.3) and Clinical Studies (14)]. As in adults, the dosage of BASAGLAR must be individualized in pediatric patients (age 6 to 15 years) with Type 1 diabetes based on metabolic needs and frequent monitoring of blood glucose.*
>
> *In the pediatric clinical trial, pediatric patients (age 6 to 15 years) with Type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia compared to the adults in trials with Type 1 diabetes [see Adverse Reactions (6.1)].*

2. Interchangeability

The sponsor agrees that Abasria and Lantus® are not interchangeable (). As stated in the Precautions section of the proposed Abasria PI:

> *The level of comparability that has been shown is not sufficient to designate this product as a generic version of Lantus. Replacement of Lantus with Abasria, or vice versa, should take place only under the supervision of a health care professional.*

What is being referenced in the topic for discussion is switching and the sponsor agrees that any change of insulin should be done under medical supervision as per the Precautions section of the proposed Abasria PI:

> *Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue), or method of manufacture may result in the need for a change in dose.*

Importantly, both Phase III studies provided data on patients switching from Lantus to Abasria at the same dose regimen; no difference in dose changes after titration to tighten glucose blood control was reported between the 2 treatment arms. Subgroup analyses based on prestudy insulin indicated no clinically relevant effect on selected safety and efficacy outcomes.

3. Clarifications

The sponsor notes 2 corrections that should be made to the Request for ACPM's Advice document:

• In Section *Insulin Antibodies*, it is incorrectly stated that there was a difference in the proportion of patients with detectable antibodies for insulin-naïve patients (e.g., overall [anytime] at 24 weeks: Abasria 19% versus Lantus 8%) in Study I4L-MC-ABEC (ABEC). This difference was observed in the subgroup of prior Lantus® patients in Study ABEC. The difference in the prior Lantus® subgroup is difficult to interpret given the small number of patients in this subgroup who had detectable antibodies at any point during the study (n=40). It is noteworthy to mention that this difference was not observed in the entire Full Analysis Set population or in the subgroup of insulin-naïve patients in Study ABEC. Also, no difference was found in Study I4L-MC-ABEB, which was the study with the most sensitive population for detecting immunogenicity (Type 1 diabetes mellitus).

• In *Discussion*; regarding the topic of non-inferiority, it is correctly stated that the 95% confidence interval did not include the non-inferiority margin of 0.3%; however, it is not entirely accurate to state that these were not corrected for multiplicity. It was not necessary to adjust for multiplicity due to the gatekeeping procedure for non-inferiority for the 24-week endpoint of both studies.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new biosimilar medicine.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Abasria, Abasria KWIKPEN, solution for injection as pre-filled syringe or pre-filled pen, containing 100 IU/mL of insulin glargine to have an overall positive benefit–risk profile for the indication**:**

> *For the treatment of Type 1 diabetes mellitus in adults and children 2 years and above and Type 2 diabetes mellitus in adults who require insulin for the control of hyperglycaemia.*

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA,
- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- Change the wording in the CMI under *How Much to Use,* which states;

  '*…do not change your insulin unless your doctor tells you. Be very careful if you do change insulin*'

  to the wording in the Lantus CMI:

  '*It is very important that you manage your diabetes carefully. Too much or too little insulin can cause serious effects'.*

  The ACPM considered that the current wording is unclear whether the change is referring to the dose or the brand of insulin. It is clear in the Lantus CMI that change is referring to dose, which is appropriate as it is under '*How Much to Use*'. However, consumers should also be made aware that they should not switch brands of insulin glargine unless under proper supervision as products are not equivalent.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- *Does the ACPM consider that the PK/PD studies provide sufficient evidence to establish that Abasria has a PK/PD profile similar to that of Lantus*?

  The ACPM advised that acceptable similarity between Abasria and Lantus has been demonstrated by the PK and PD studies.

- *Does the ACPM consider that the Phase III studies provide sufficient evidence to establish that immunogenicity is similar to Lantus*?

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.

- *Studies of similarity between Abasria and Lantus have been conducted in adults. Does the ACPM consider that these allow extrapolation of the similarity to children, 2 years and older?*

  The ACPM noted that Lantus is registered for use in children from the age of 2 years but has not been studied in children less than 2 years of age. Therefore, as Abasria has been accepted as similar to Lantus, the ACPM advised that extrapolation can be allowed for use in children 2 years and older.

- *Biosimilars are not regarded as interchangeable on a same-dose basis with the reference product. That is, any switch from Lantus to Abasria should only be done under medical supervision and may require different dosing and particular caution regarding hypoglycaemia. Does the ACPM consider that the information provided in the PI is appropriate?*

  The ACPM advised that the statement regarding switching between the two products is appropriate.

  The ACPM also considered that an educational program for health professionals may be needed to highlight that any product switching must be supervised and dose equivalence should not be assumed for any individual patient.

  The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of to approve the registration of Abasria insulin glargine (the) 100 IU/mL solution for Injection cartridge Abasria KwikPen insulin glargine (the) 100 IU/mL solution for injection cartridge for subcutaneous injection, indicated for:

> *Insulin glargine 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.*

Specific conditions of registration applying to these goods

1. The Abasria (insulin glargine) EU Risk Management Plan Version 1.0 dated 22 May 2013, [data lock point (DLP) 01 April 2013] and Australian Specific Annex Version 2 dated 21 May 2014, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. As a minimum, the first five independent batches of Abasria (insulin glargine (rbe)) solution for injection in cartridge and prefilled pen 100 IU/mL imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

Attachment 1. Product Information

The Product Information approved for main Abasria at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au