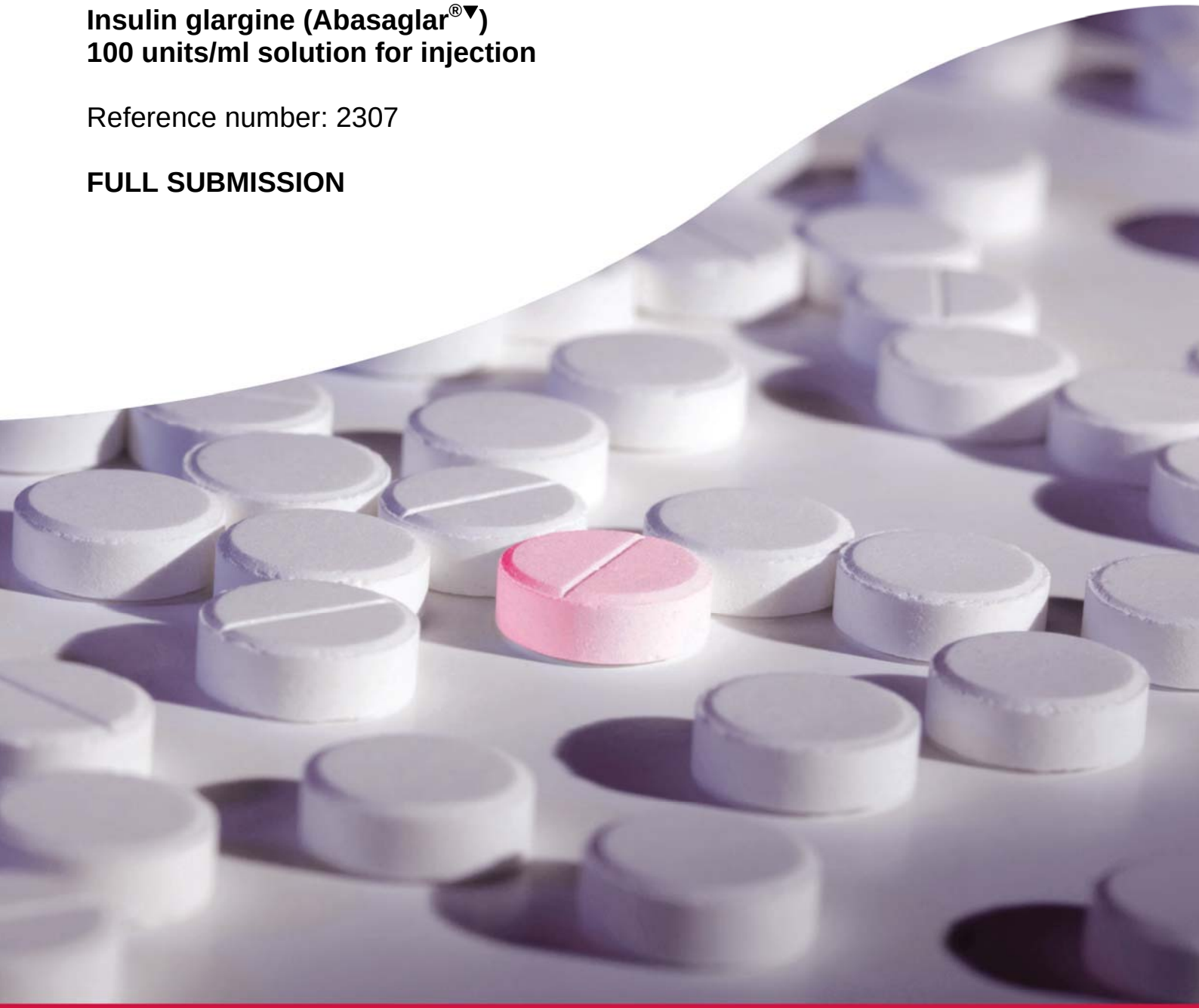
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Insulin glargine (Abasaglar®▼)
100 units/ml solution for injection

Reference number: 2307

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Insulin glargine (Abasaglar®▼) 100 units/ml solution for injection. Reference number: 2307. October 2015.

AWMSG Secretariat Assessment Report
Insulin glargine (Abasaglar®▼) 100 units/ml solution for injection

This assessment report is based on evidence submitted by Boehringer Ingelheim and Eli Lilly & Co Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Insulin glargine (Abasaglar®▼) for the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above[2].
Dosing	Abasaglar®▼ should be administered subcutaneously once daily at any time, but at the same time each day. Dose and timing should be individually adjusted. Refer to the Summary of Product Characteristics for further information regarding administration[2].
Marketing authorisation date	9 September 2014[2].
UK launch date	September 2015[1].

2.0 DECISION CONTEXT

2.1 Background

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by high levels of blood glucose (hyperglycaemia) which can, if prolonged, cause microvascular and macrovascular damage in the body[3,4]. The National Institute for Health and Care Excellence (NICE) Clinical Guidelines (CGs) recommend initiating insulin therapy with Neutral Protamine Hagedorn (NPH) insulin and, consider as an alternative, using a long-acting insulin analogue under certain circumstances (e.g. when hypoglycaemia is a problem)[3,5,6].

Abasaglar®▼ is a European Medicines Agency (EMA) approved biosimilar medicine of insulin glargine (Lantus®), a long-acting insulin analogue[7]. A biosimilar medicine is a biological medicine developed to be similar to an existing biological medicine (the reference medicine)[8]. The active substance of the biosimilar and its reference medicine is essentially the same substance, though due to the complex nature and production of the product there may be minor differences[8]. The licensed therapeutic indication, dosing regimen, pharmaceutical form and strength of Abasaglar®▼ are the same as those of Lantus®[7].

The company submission focuses on the use of Abasaglar®▼ within its licensed indication, from age 2 years and above, in line with the current use of Lantus® in clinical practice in Wales and for which positive NICE and All Wales Medicines Strategy Group (AWMSG) guidance exists[3,5,6,9].

2.2 Comparators

The comparator included in the company submission is Lantus®, the reference medicine for Abasaglar®▼[1,7].

2.3 Guidance and related advice

- NICE. Pathway: blood-glucose-lowering therapy for type 2 diabetes (2015)[10].
- Welsh Government. Together for Health - a diabetes delivery plan. A delivery plan up to 2016 for NHS Wales and its partners (2013)[11].
- NICE. CG87. Type 2 diabetes: the management of type 2 diabetes (2009)[6].
- Welsh Assembly Government. Designed for the management of adults with diabetes mellitus across Wales: consensus guidelines (2008)[12].
- NICE. CG15. Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults (2004)[5].
- NICE. Technology Appraisal 53. Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine (2002)[3].

AWMSG has previously issued a recommendation for the use of insulin glargine (Lantus®)[9].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

Pharmacokinetic (PK) and pharmacodynamic (PD) equivalence of Abasaglar®▼ and Lantus® has previously been established based on a comparability exercise performed in five studies, which tested several dose levels and were conducted in healthy volunteers and patients with type 1 DM (T1DM)[7].

The company submission includes details of two phase III studies, ELEMENT-1 and ELEMENT-2, aimed at demonstrating noninferiority of Abasaglar®▼ to Lantus®[1].

3.1 ELEMENT-1

ELEMENT-1 was a prospective, randomised, open label, multicentre, two-arm, active-control, parallel study with a 24 week treatment period, followed by a 28 week extension period and four weeks of post-treatment follow-up[1,7,13]. Patients had T1DM and had been on basal-bolus insulin therapy for at least one year prior to study entry. Patients were randomised to once daily Abasaglar®▼ (n = 268) or once daily Lantus® (n = 267) in combination with pre-meal insulin lispro administered three times a day[1,7,13].

Primary endpoint was the change in glycosylated haemoglobin (HbA_{1c}) levels from baseline to 24 weeks, or last observation carried forward, based on the full analysis set[1,7,13]. Secondary endpoints included change in HbA_{1c} at other intermediate time points, blood glucose levels, basal insulin dose, weight and safety[1,7,13].

There was a statistically significant decrease in HbA_{1c} from baseline to 24 weeks in both the Abasaglar®▼ and Lantus® treatment groups ($p < 0.001$)[1,7,13]. Abasaglar®▼ was found to be noninferior to Lantus® at the 0.4% and 0.3% noninferiority margins. Noninferiority of Abasaglar®▼ to Lantus® was confirmed at 52 weeks. See Table 1 for results. Overall, secondary endpoints supported the conclusion of equivalent efficacy between Abasaglar®▼ and Lantus®[1,7,13].

3.2 ELEMENT-2

ELEMENT-2 had a similar study design as ELEMENT-1, but was double-blind and did not include a 28 week extension period[1,7,14]. Patients had type 2 DM (T2DM) and had either failed to achieve adequate glycaemic control with at least two oral antidiabetic medications (OAMs) and were insulin-naïve at baseline, or were already taking Lantus® in combination with at least two OAMs and had adequate or inadequate glycaemic control. Patients were randomised to once daily Abasaglar®▼ (n = 376) or once daily Lantus® (n = 380) in combination with pre-study OAMs at the same dose[1,7,14].

Primary and secondary endpoints were the same as those in ELEMENT-1[1,7,14].

Results were similar to those observed in patients with T1DM in the ELEMENT-1 study (Table 1). There was a statistically significant decrease in HbA_{1c} from baseline to 24 weeks in both the Abasaglar®▼ and Lantus® treatment groups ($p < 0.001$)[1,7,14]. Abasaglar®▼ was noninferior to Lantus® at the 0.4% and 0.3% noninferiority margins. Overall, secondary endpoints further supported the conclusion of equivalent efficacy between Abasaglar®▼ and Lantus®[1,7,14].

Table 1. Summary of change in HbA_{1c} (mmol/mol) for ELEMENT-1 and ELEMENT-2.

	ELEMENT-1				ELEMENT-2	
	24 weeks		52 weeks		24 weeks	
Mean HbA_{1c} (mmol/mol)	Abasaglar®▼	Lantus®	Abasaglar®▼	Lantus®	Abasaglar®▼	Lantus®
LSM change from baseline (SE)	−4 (1)	−5 (1)	−3 (1)	−3 (1)	−14 (1)	−15 (1)
LSM difference (95% CI)	1.2 (−0.1 to 2.4)		0.2 (−1.1 to 1.5)		0.6 (−0.8 to 1.9)	
p-value	¶		¶		¶	

¶: commercial in confidence figure removed.

CI: confidence interval; HbA_{1c}: glycosylated haemoglobin; LSM: least-squares mean; SD: standard deviation; SE: standard error.

3.3 Safety

The company submission includes safety data up to 12 months from ELEMENT-1 and six months from ELEMENT-2[1]. Overall, the safety profile of Abasaglar®▼ was similar to that of Lantus® and in line with the safety characteristics expected from an insulin product[1,7]. There were no major safety findings or signals identified[7]. Rates of treatment-emergent adverse events (TEAEs) were similar across the Abasaglar®▼ and Lantus® treatment groups with one exception: vascular disorders (primarily hypertension) in ELEMENT-2 (21 patients [5.6%] in the Abasaglar®▼ group versus nine patients [2.4%] in the Lantus® group [commercial in confidence figure removed])[1,7]. The Committee for Medicinal Products for Human Use (CHMP) concluded that this significant difference was likely due to more patients randomised to the Abasaglar®▼ treatment group with pre-existing hypertension rather than a causal link. There were no differences in the rates of serious adverse events (SAEs) and deaths. Hypoglycaemia was the most frequent SAE in both studies[1,7].

3.4 AWTTC critique

- CHMP concluded that all major physicochemical characteristics and biological activities demonstrated biosimilar comparability between Abasaglar®▼ and the reference medicine, Lantus®[7].
- The company suggest that Abasaglar®▼ should be available as a treatment option for both T1DM and T2DM patients who are eligible for treatment with Lantus® in line with current guidance and Welsh clinical practice[1,3,5,6,9]. Current guidance recommends initiating insulin therapy with NPH insulin and, consider as an alternative, using a long-acting insulin analogue under certain circumstances (e.g. when hypoglycaemia is a problem)[3,5,6]. Clinical expert opinion sought by the All Wales Therapeutics and Toxicology Centre (AWTTC)

confirms this is in line with Welsh clinical practice and Lantus® is the most commonly prescribed long-acting insulin analogue.

- Abasaglar®▼ is available in two presentations: a cartridge for delivery by a reusable pen (Savvio™) and a disposable prefilled pen (KwikPen™)[2]. Lantus® is similarly available as a cartridge for delivery by a reusable pen[15] and prefilled pen[16], but is also available as a vial[17].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] includes a cost-minimisation analysis (CMA) of Abasaglar®▼ within the licensed indication for which positive NICE/AWMSG guidance exists for the reference product Lantus®, each administered via pen or cartridge. The administration of Lantus® via vial and syringe is not included in the analysis. The applicant company has adopted a CMA approach on the basis that CHMP concluded Abasaglar®▼ is a biosimilar to the reference product, and in both phase III studies Abasaglar®▼ was found to be noninferior to Lantus®.

The CMA considers the acquisition costs of both Abasaglar®▼ and Lantus®, daily unit requirements for both T1DM and T2DM, and monitoring and administration costs. Acquisition costs were sourced from the British National Formulary (BNF)[18]. The average daily dose for patients in the UK was obtained from a NICE appraisal on long-acting insulin analogues[3]. Monitoring and administration costs were taken from a recent cost-effectiveness study[19]. An NHS Wales and Personal Social Services perspective for costing was adopted and the time horizon used to calculate the annual incremental differences in cost per patient treated was one year; consequently no discount rate was applied. Subgroup analysis provided insight into the costs associated with T1DM and T2DM, given that daily dosing is different between these patient groups. The company has not provided any sensitivity analyses.

4.1.2 Results

The results of the base case and subgroup analyses are presented in Table 2. In terms of average annual medicine acquisition costs of treatment, the incremental difference in acquisition costs results in an annual average cost saving of £49.43 per patient treated with Abasaglar®▼. The monitoring and administration costs are reported as equal for both treatments. Subgroup analyses indicate annual cost savings of £38.02 and £60.83 for T1DM and T2DM patients, respectively.

Table 2. Key results of the base case and subgroup analyses.

	Abasaglar®▼	Lantus®	Difference
Base-case analysis			
Medicine acquisition cost per pen/cartridge	£7.05	£8.30	−£1.25
Average annual acquisition cost	£278.77	£328.20	−£49.43
Monitoring and administration cost	£155.17	£155.17	0
Scenario and subgroup analyses			
Annual acquisition cost (T1DM)	£214.44	£252.46	−£38.02
Annual acquisition cost (T2DM)	£343.10	£403.93	−£60.83
T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus.			

4.1.3 AWTTC critique

The CMA approach assumes equivalence in all domains of health outcomes. The EMA has approved Abasaglar®▼ as a biosimilar medicine to Lantus® based on five relevant

PD/PK studies that showed equivalence of the two medicines within predefined bioequivalence levels. The two phase III studies evaluating efficacy and safety also found Abasaglar®▼ to be noninferior to Lantus®.

Strengths and limitations of the economic analysis are as follows:

- The use of CMA in the comparison of Abasaglar®▼ and Lantus® appears justifiable as the two treatments were found to have similar PK and PD profiles in bioequivalence studies.
- The submission gives a detailed and transparent account of the methods, data sources and analyses undertaken.
- The time horizon and perspective used for the CMA both appear appropriate.
- While the use of Lantus® as the main comparator is appropriate, costing is limited to pens and cartridges only. Lantus® is also available in vial form. For the sake of transparency, and to reflect current practices, the inclusion of this additional method of administration would have been beneficial. However, given that the unit cost of vials exceeds that of prefilled pens/cartridges, its exclusion from the analysis likely results in an underestimation of the cost of Lantus® and likewise the proposed savings associated with Abasaglar®▼.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Prevalence data for Wales were sourced from Diabetes UK[20,21]. There are 173,299 patients with DM in Wales[20]; 10% of this population have T1DM, 90% have T2DM[21]. All T1DM patients and approximately 30% of T2DM patients require administration of insulin[3]. Of these patients, it is assumed approximately 60% of both T1DM and T2DM require long-acting analogue insulin[6] and [commercial in confidence figure removed] of these are prescribed Lantus®. Abasaglar®▼ is expected to only be prescribed to a percentage of annual new initiators to Lantus®. New initiators are defined as patients that are insulin naive or patients that require intensification of treatment as a result of inadequate glycaemia control. Of the new initiators, Abasaglar®▼ is assumed to have 4% market share in year 1, rising to 18% in year 5. The company anticipates that new initiators will continue to be treated in subsequent years. Thus the number of patients in years 2–5 consists of new initiators plus currently treated patients.

In addition to those already mentioned, the budget impact analysis is guided by a number of key assumptions, including:

- A constant rate of 0.27% population growth in Wales over the next five years[22].
- Constant incidence rates for T1DM and T2DM at 24.5 cases per 100,000 individuals aged 0–14 years, and 515 cases per 100,000 individuals respectively, over the next five years[21].
- Constant mortality rates of 9.17% and 2.24% for T1DM and T2DM patients respectively, over the next five years[23].
- 69% of insulin analogue patients currently receive Lantus®[1].
- A rate of T2DM new initiators to Lantus® of [commercial in confidence figure removed] per 100 current Lantus® users.
- The current use of Lantus® vials is 0%.

Four one-way sensitivity analyses explore how sensitive the budget impact model is to changes in: prevalence of DM, the percentage of patients with T2DM requiring insulin, the market share of Lantus®, and the incidence rate of new initiation to Lantus®.

5.1.2 Results

The estimated costs savings generated by the CMA are multiplied by the eligible population over the next five years to calculate budget impact. The administration and

monitoring costs of both treatments are assumed to be equal. Table 3 therefore details the projected five year budget impact on the basis of acquisition costs only. Table 4 presents a breakdown of the estimated costs of both treatments on a yearly basis for the next five years. Table 5 details the results of the sensitivity analyses conducted.

Table 3. Estimated five year budget impact of providing Abasaglar®▼ to eligible T1DM and T2DM patients in Wales.

Budget Impact Results	Abasaglar®▼	Lantus®	Difference
Five year budget impact (T1DM)	£17,319.26	£20,390.05	−£3,071
Five year budget impact (T2DM)	£1,081,319.30	£1,273,042.58	−£191,723
Five year total budget impact	**£1,098,639**	**£1,293,433**	**−£194,794**
T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus.			

Table 4. Company-reported costs associated with use of Abasaglar®▼ for the treatment of patients with T1DM and T2DM eligible to be new initiators to Lantus®.

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Number of eligible patients	2,280	2,286	2,293	2,299	2,305
Uptake (%)	4	8	13	16	18
Treated patients	91	274	572	940	1,355
Net costs					
Lantus® costs	£36,499	£109,694	£228,955	£376,133	£542,152
Abasaglar®▼ costs	£31,002	£93,173	£194,474	£319,487	£460,502
Administration and monitoring	£14,154	£42,537	£88,785	£145,857	£210,236
Overall net cost	**−£5,497**	**−£16,520**	**−£34,481**	**−£56,647**	**−£81,649**

Table 5. Results of the four one-way sensitivity analyses.

Univariate sensitivity analyses	Range	Range justification	5 year budget impact
SA1 - Welsh DM prevalence	6.7%	Diabetes UK estimate[21]	−£229,318
SA2 -Insulin use in T2DM patients	15%–45%	–	−£98,932 to −£290,656
SA3 - Lantus® current market share	35%–100%	–	¶
SA4 - New initiators to Lantus®	5%–20%	–	−£98,932 to −£365,521
¶: commercial in confidence figures removed. SA: sensitivity analysis; DM: diabetes mellitus; T2DM: type 2 diabetes mellitus.			

5.1.3 AWTTC critique

Strengths and limitations of the budget impact analysis are as follows:

- The submission gives a detailed and transparent account of the methods and data sources used in the budget impact analysis.
- The sensitivity analyses explore the assumptions made in relation to model parameters and uncertainties. Whilst such analyses are generally beneficial, it is not clear how the ranges for market share and new initiators to Lantus® for T2DM patients have been selected. It is therefore unclear how realistic the forecasted net savings are.
- The budget impact model is limited to exploring Abasaglar®▼ as a treatment option for new initiators to Lantus® only. This limits the application of the budget

impact to a smaller subset of patients. The company state that they will not support switching from Lantus® to Abasaglar®▼ as they are only aiming at new initiators of insulin therapy. This is generally supported by clinical expert opinion sought by AWTTC.

5.2 Comparative unit costs

Examples of annual acquisition costs for Lantus® and the biosimilar Abasaglar®▼ are detailed in Table 6.

Table 6. Comparative acquisition costs for Abasaglar®▼ and its reference product.

Medicine	Frequency and route of administration	Approximate annual cost per patient (cost per cartridge/3 mls)
Insulin Glargine (Abasaglar®▼) 100 units/ml in a 3ml pre-filled pen or cartridge	Once daily subcutaneous injection	£278.77 (£7.05)
Insulin Glargine (**Lantus®**) 100 units/ml in a 3ml pre-filled pen or cartridge	Once daily subcutaneous injection	£328.20 (£8.30)
Insulin Glargine (**Lantus®**) 100 units/ml in a 10ml vial	Once daily subcutaneous injection	£363.94

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, insulin glargine (Abasaglar®▼) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation or by Practitioners with a special interest in diabetes mellitus.

The company do not anticipate that insulin glargine (Abasaglar®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted one ongoing study that is likely to be available within 6–12 months. ELEMENT-5 (trial ID: NCT02302716) is a prospective, open label, randomised noninferiority comparison of Abasaglar®▼ with Lantus® in adults with T2DM in India and Russia with a treatment period of 24 weeks. The proposed end date is July 2016.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 23, 24 and 29 June 2015.
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Boehringer Ingelheim and Eli Lilly & Co Ltd. Form B: Detailed appraisal submission. Insulin glargine (Abasaglar®▼). May 2015.

2 Eli Lilly & Co Ltd. Abasaglar®▼. Summary of Product Characteristics. Jun 2015. Available at: http://www.medicines.org.uk/emc/medicine/30494. Accessed Jul 2015.

3 National Institute for Health and Care Excellence. Technology Appraisal 53. Guidance on the use of long-acting insulin analogues for the treatment of diabetes - insulin glargine. Dec 2002. Available at: http://www.nice.org.uk/guidance/ta53. Accessed Jun 2015.

4 Welsh Government. National service framework for diabetes (Wales): standards. Mar 2005. Available at: http://wales.gov.uk/docs/dhss/publications/100930diabetesen.pdf. Accessed Jun 2015.

5 National Institute for Health and Care Excellence. Clinical Guideline 15. Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults. Jul 2004. Available at: http://www.nice.org.uk/guidance/cg15. Accessed Jun 2015.

6 National Institute for Health and Care Excellence. Clinical Guideline 87. Type 2 diabetes: the management of type 2 diabetes. May 2009. Available at: http://www.nice.org.uk/guidance/cg87. Accessed Jun 2015.

7 European Medicines Agency. Assessment Report: Abasria. Procedure No.: EMEA/H/C/002835/0000. Jun 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002835/WC500175383.pdf. Accessed Jun 2015.

8 European Medicines Agency. Questions and answers on biosimilar medicines (similar biological medicinal products). Sep 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf. Accessed Jun 2015.

9 All Wales Medicines Strategy Group. Insulin glargine (Lantus®) 100 units/ml solution for injection. Reference No. 1673. Appraisal information. Mar 2013. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1673. Accessed Jun 2015.

10 National Institute for Health and Care Excellence. Pathway: blood-glucose-lowering therapy for type 2 diabetes. Mar 2015. Available at: http://pathways.nice.org.uk/pathways/diabetes/blood-glucose-lowering-therapy-for-type-2-diabetes. Accessed Jun 2015.

11 Welsh Government. Together for health - a diabetes delivery plan. A delivery plan up to 2016 for NHS Wales and its partners. 2013. Available at: http://wales.gov.uk/docs/dhss/publications/130923diabetesen.pdf. Accessed Jun 2015.

12 Welsh Assembly Government. Designed for the management of adults with diabetes mellitus across Wales: consensus guidelines. Oct 2008. Available at: http://www.wales.nhs.uk/sitesplus/documents/861/Designed%20for%20the%20Management%20of%20Adults%20with%20Diabetes%20Mellitus%20across%20Wales1.pdf. Accessed Jun 2015.

13 Blevins TC, Dahl D, Rosenstock J et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. *Diabetes, Obesity and Metabolism* 2015; 17 (8): 726-33. Available at: http://onlinelibrary.wiley.com/doi/10.1111/dom.12496/pdf. Accessed: Sep 2015.

14 Rosenstock J, Hollander P, Bhargava A et al. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study). *Diabetes,*

Obesity and Metabolism 2015; 17 (8): 734-41. Available at: http://onlinelibrary.wiley.com/doi/10.1111/dom.12482/epdf. Accessed: Sep 2015.
15 Sanofi-Aventis Ltd. Lantus® 100 units/ml solution for injection in a cartridge. Summary of Product Characteristics. Jul 2015. Available at: http://www.medicines.org.uk/emc/medicine/25507. Accessed Jul 2015.
16 Sanofi-Aventis Ltd. Lantus® SoloStar® 100 units/ml solution for injection in a pre-filled pen. Summary of Product Characteristics. Jul 2015. Available at: http://www.medicines.org.uk/emc/medicine/20123. Accessed Jul 2015.
17 Sanofi-Aventis Ltd. Lantus® 100 units/ml solution for injection in a vial. Summary of Product Characteristics. Jul 2015. Available at: http://www.medicines.org.uk/emc/medicine/25506. Accessed Jul 2015.
18 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. Jul 2015. Available at: https://www.medicinescomplete.com/mc/bnf/current/. Accessed Jul 2015.
19 Evans M, Wolden M, Gundgaard J et al. Cost-effectiveness of insulin degludec compared with insulin glargine in a basal-bolus regimen in patients with type 1 diabetes mellitus in the UK. *Journal of Medical Economics* 2015; 18 (1): 56-68. Available at: http://informahealthcare.com/doi/pdf/10.3111/13696998.2014.971160. Accessed: Jul 2015.
20 Diabetes UK. State of the Nation: Wales 2013-14. Nov 2013. Available at: https://www.diabetes.org.uk/Upload/Wales/Website%20NEW/Diabetes%20In%20Wales/Healthcare%20Policy%20In%20Wales/State%20of%20The%20Nation%202013%20-%20Wales.pdf. Accessed Jul 2015.
21 Diabetes UK. Diabetes in the UK 2013. Key statistics on diabetes. Mar 2014. Available at: https://www.diabetes.org.uk/Documents/About%20Us/Statistics/Diabetes-key-stats-guidelines-April2014.pdf. Accessed Jun 2015.
22 Office of National Statistics. Population estimates for UK, England and Wales, Scotland and Northern Ireland, mid-2013 - superseded. Jun 2014. Available at: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/2013/index.html. Accessed Jul 2015.
23 The Health and Social Care Information Centre (HSCIC). National diabetes audit 2012-2013. Report 2: complications and mortality. 2015. Available at: http://www.hscic.gov.uk/catalogue/PUB16496/nati-diab-audi-12-13-rep2.pdf. Accessed Jul 2015.