East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Surrey Prescribing Clinical Network

Medicine and proposed indication	Insulin Glargine Biosimilar Abasaglar®
Requested by	

SUMMARY

Clinical Effectiveness

Insulin glargine is a human insulin analogue for basal insulin use. Abasaglar is an insulin glargine biosimilar product containing 100 units/ml solution for injection in a cartridge and a pre-filled pen[1].

The clinical effectiveness to show biosimilarity between Abasaglar and Lantus is based on five phase 1 and two phase 3 studies. The phase 1 studies primarily assessed pharmacokinetic parameters. Pharmacokinetic equivalence of the two insulins was convincingly demonstrated across all studies and all doses using methodology in line with Committee for Medicinal Products for Human Use (CHMP) [2] guidance.

Phase 1 trials[3-5]:

- Overall these phase 1 studies showed Abasaglar® and Lantus to have similar pharmacokinetic and pharmacodynamic profiles. The mean duration of action for both was very similar - 24 and 26 hours for Abasaglar® and Lantus, respectively.

Phase 3 trials[6-7]:

ELEMENT-1 was a 52-week, randomised, open-label study of 535 patients with T1DM. Patients in the study were also treated with mealtime insulin.26
ELEMENT-2 was a 24-week, randomised, double-blind study of 756 patients with T2DM inadequately controlled on two or more oral diabetes medicines.27
The primary objective in both studies was to evaluate whether Abasaglar® was non-inferior to Lantus in reducing average HbA1c levels from baseline at 24 weeks.

- In both studies, neither product demonstrated non-inferiority to the other. A similar reduction in HbA1c from baseline to 24 weeks was seen in both treatment groups, with a difference between groups of 0.11% (1.20 mmol/mol), 95% confidence intervals (CI) −0.00 to 0.22 (−0.00 to 2.40 mmol/mol) in ELEMENT 1 and 0.05% (0.60 mmol/mol), 95% CI −0.07 to 0.18 (−0.80 to 1.90 mmol/mol) in ELEMENT 2. The treatment difference was below the pre-specified non-inferiority margins of 0.4% and 0.3% in both studies.
- ELEMENT 1, was continued to 52 weeks and non-inferiority of Abasaglar to Lantus was confirmed at this further time point.
- There were also no statistically significant treatment differences in either study for secondary outcomes such as the proportion of participants meeting HbA1c targets or the mean change in body weight between people using Abasaglar and those using Lantus.
- The European public assessment report (EPAR)[9] states that both studies provided data on patients switching from Lantus to Abasaglar at the same dose regimen, and no difference in dose changes after titration to tighten blood glucose control was reported between the 2 treatment arms further reinforcing their non-inferiority with each insulin.

Safety

- In the phase III studies, ELEMENT 1 and ELEMENT 2, there were no statistically significant differences between treatment groups in the reported incidences of adverse events and serious adverse events[9].
- Total mean hypoglycaemia rates (events per person per year), as well as rates of nocturnal or severe hypoglycaemia, were not statistically significantly different between Abasaglar and Lantus in either the ELEMNET 1or the ELEMENT 2 study[10].
- There are no published clinical studies comparing Abasaglar with Lantus in children and young people. However, the summary of product characteristics includes reference to paediatric studies with Lantus.
- Medication errors are an important risk with insulin glargine biosimilar (Abasaglar) 100 units/ml. The MHRA Drug safety update [10]advises that healthcare professionals and people with diabetes should understand the differences between Abasaglar and several other new insulin products that have recently become available.
- The European public assessment report (EPAR) [8] states that the number of allergic events and injection site-related abnormalities appeared similar between the 2 insulins and were considered acceptable.
- Both studies provided data on patients switching from Lantus to Abasaglar at the same dose regimen, and no difference in dose changes after titration to tighten blood glucose control was reported between the 2 treatment arms in the EPAR[9].
- The immunogenicity profiles of Abasaglar and Lantus were comparable up to the 52-week end point. In ELEMENT 1 a total of 212 participants (39.8%) had detectable antibodies to insulin at 52 weeks and in ELEMENT 2, 96 participants (13.2%) had detectable antibodies to insulin at 24 weeks, with no statistically significant difference between treatment groups.
- In both ELEMENT 1 and ELEMENT 2 similar numbers of people withdrew because of adverse events in both treatment groups[9].
- The primary amino acid sequence of Abasaglar® is the same as that of the active ingredient in Lantus. Abasaglar® has the same pharmaceutical form and strength as Lantus. Abasaglar® differs from the reference medicinal product with respect to excipients used in the formulation: In Abasaglar® zinc oxide replaces zinc chloride and 100% glycerol is used compared with 85% in the reference medicinal product[9].
- The Abasaglar summary of product characteristics lists the same contraindications, cautions and undesirable effects as for Lantus and lists hypoglycaemia as a very common adverse reaction[1, 11].
- In the UK, the MHRA recommends that all biological medicines, including biosimilar medicines, are prescribed by brand name[12].

Patient factors

- Abasaglar is given once daily by subcutaneous injection, and is available as 100 units/ml in cartridges or as a pre-filled pen[1].
- Across the 2 RCTs similar numbers of people withdrew because of adverse events with Abasaglar compared with Lantus (1% compared with 2% in people with type 1 diabetes and 2% compared with 3% in people with type 2 diabetes).
- Abasaglar is a new insulin product and people with diabetes need to understand the differences between Abasaglar and several other new insulin products that have recently become available to minimise the risk of medication error[10]. The choice of whether a patient receives a biosimilar or originator biological medicine rests with the responsible clinician in consultation with the patient.

Cost implications

Biosimilars have the potential to offer the NHS considerable cost savings, especially as biological medicines are often expensive and are often used to treat long-term conditions.

The cost of Abasaglar and other basal insulins depends on the preparation chosen and the insulin dosage used. The list price of Abasaglar is about 15% lower than Lantus.

There is no specific guidance available on substitution of the reference product (Lantus®) with the biosimilar (Abasaglar®). This will however require blood glucose monitoring and may potentially require dosage adjustment.

In the phase III trials ELEMENT 1 and 2, there was a subgroup that was switched from Lantus to Abasaglar at the same dose regimen and no difference in dose changes after titration to tighten glucose blood control was reported between the two treatment arms. However, in a drug safety update the MHRA advised that some dose adjustment may be needed for some patients[10].
The manufacturer of Abasaglar is not promoting a switch from insulin glargine to Abasaglar but a switch programme locally could be something CCGs may want to produce.

It is estimated using ePACT data that a one hundred per cent switch across England and Wales could save over £12 million. This equates to £19,926 per 100,000 patients. (ePACT data July - September 2015).

Total Glargine prescribing for 14.15 is approx £1.87M (5 surrey CCG's)

Prescriber Name	Potential Yearly Savings when 15% glargine switched to Abasaglar
NW Surrey CCG	£110,217.42
PCT SURREY DOWNS CCG	£43,349.18
PCT EAST SURREY CCG	£35,441.43
PCT GUILDFORD AND WAVERLEY CCG	£29,457.82
PCT SURREY HEATH CCG	£23,548.19
	£242,014.05

Relevant guidance / reviews

-NICE Evidence Summary; Diabetes mellitus type 1 and type 2: insulin glargine biosimilar (Abasaglar) NICE advice [ESNM64] published December 2015.

-MHRA Drug Safety Update April 2015 High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error

-European Medicines Agency. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues. February 2015.

-UKMI In Use Safety assessment report for Toujeo and Abasaglar (insulin glargines)[13]

-London Medicines Evaluation Network Review : Answers to commonly asked questions about

biosimilar versions of insulin glargine, October 2015[14]

-Scottish Medicines Consortium (SMC) Policy Statement [15]

The SMC believes that the managed introduction of biosimilar medicines into clinical practice in NHS Scotland is desirable. To facilitate this process, from May 2015 the SMC will no longer routinely assess biosimilar medicines on the basis of a full submission. These products will be considered 'out of remit' where the reference product has been accepted by SMC/Health Improvement Scotland (HIS) for the same indication(s) and in the same population or was initially licensed and available prior to 31 January 2002.

-NICE NICE advice [KTT15]: Biosimilar Medicines Published date: February 2016[16]

Likely place in therapy relative to current treatments

There are no more biosimilar insulins that are to come onto the market in the next year or so. There is one insulin glargine that has entered phase 3 development six months ago.

Abasaglar has been shown in trials to be non-inferior to insulin Glargine. Abasaglar is licensed for the same indication as Lantus (treatment of diabetes mellitus in adults, young people and children aged 2 years and above) and the summary of product characteristics includes the same contraindications and warnings. Therefore, the place in therapy should be the same as that for insulin glargine.

For patients with Type 1 diabetes, the NICE[17] recommend that once-daily insulin glargine can be considered if twice daily insulin detemir, the preferred basal insulin therapy, is not tolerated.

In patients with type 2 diabetes when insulin therapy is necessary (NG28[19]), it should be started from a choice of a number of insulin types and regimens. NPH insulin injected once or twice daily according to need is the preferred basal insulin. Insulin detemir or insulin glargine can be considered as an alternative for some people in certain situations :

- the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily **or**
- the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes **or**
- the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs

Recommendation to PCN

Options include:

1. Approve for use in line with NICE guidelines 17 and 28 for new patients where insulin glargine is required.
2. Consider a local switch programme for patients who may be appropriately switched from insulin glargine to Abasaglar.

Medicine details[1]	
Name and brand name	Abasaglar® 100 units/mL solution for injection in a cartridge: 3 mL cartridge, for delivery by a reusable pen injector (HumaPen Savvio). Each mL contains 100 units insulin glargine (equivalent to 3.64 mg). Each cartridge contains 3 mL of solution for injection, equivalent to 300 units. Abasaglar 100 units/mL solution for injection in a pre-filled pen: 3 mL cartridge sealed in a prefilled pen injector (KwikPen). Each pen contains 3 mL of solution for injection, equivalent to 300 units
Licensed indication, formulation and usual dosage	Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above. Abasaglar should be administered once daily at any time but at the same time each day. The dose regimen (dose and timing) should be individually adjusted. In patients with type 2 diabetes mellitus, Abasaglar can also be given together with orally active antidiabetic medicinal products
Monitoring requirements	All patients should routinely monitor their blood glucose levels as per the treating clinician's instructions. As per NICE NG28 :Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation) Patients with either type 1 or type 2 diabetes should be under regular review to ensure appropriate management of their diabetes and associated complications.
Prescribing considerations	Abasaglar® is an option for patients that are prescribed a long acting analogue. It is a biosimilar to Lantus® insulin glargine so should be considered as an option in new patients requiring insulin glargine in line with NICE guidelines. All insulins should be prescribed by brand name to avoid patients inadvertently being switched to a different insilin. The biosimilar product, Abasaglar®, is non-inferior and an alternative to Lantus®. Patients who are to be prescribed Abasaglar must be able to use the insulin pens currently available from Eli Lilly i.e. the KwikPen® and HumaPen Savvio®. A short or rapid acting insulin will need to be added to cover mealtime requirements in type 1 diabetes and in some type 2 diabetes patients. The choice of whether a patient receives a biosimilar or originator biological medicine rests with the responsible clinician in consultation with the patient. Any switching from Lantus® to Abasaglar® would require a managed approach with blood glucose monitoring, since dosage adjustment could theoretically be required.

Potential patient group (if appropriate to include)	
Brief description of disease	Type 1 diabetes is a long-term hormonal deficiency disorder treated with insulin replacement therapy. This is supported by active management of other cardiovascular risk factors, such as hypertension and high circulating lipids. Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance and insufficient pancreatic insulin production, resulting in high blood glucose levels. Type 2 diabetes is commonly associated with obesity, physical inactivity, raised blood pressure and disturbed blood lipid levels, and therefore is recognised to have an increased cardiovascular risk. It is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy
Potential patient numbers per 100,000	
Outcomes required	Achieving good glycaemic control is important in minimising the risk of long-term diabetes related complications.

Summary of current treatment pathway

NICE Guideline 17[16] on the diagnosis and management of type 1 diabetes recommends the following in relation to long acting insulin:

• Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes.

• Consider, as an alternative basal insulin therapy for adults with type 1 diabetes:

- An existing insulin regimen being used by the person that is achieving their agreed targets,
- Once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person or once-daily insulin glargine if insulin detemir is not tolerated.

• Consider other basal insulin regimens for adults with type 1 diabetes only if the regimens recommendations above do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost.

The NICE clinical guideline on type 2 diabetes states[17]:

Initiate insulin therapy from a choice of a number of insulin types and regimens.

• Begin with human NPH insulin injected at bed-time or twice daily according to need.

• Consider, as an alternative, using a long-acting insulin analogue (insulin detemir, insulin glargine) if:

- The person needs assistance from a carer or healthcare professional to inject insulin, and use of

a long acting insulin analogue (insulin detemir, insulin glargine) would reduce the frequency of injections from twice to once daily, or

- The person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, or
- The person would otherwise need twice-daily NPH insulin injections in combination with oral

glucose-lowering drugs, or

- The person cannot use the device to inject NPH insulin.

Evidence review

NICE Evidence Summary ; Diabetes mellitus type 1 and type 2: insulin glargine biosimilar (Abasaglar); NICE advice [ESNM64] published December 2015[9].

Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	Basingstoke, Southampton and Winchester District Prescribing Committee have given Abasaglar a green traffic light status as have many other NHS organisations across the country such as Leeds, Derbyshire, North valley
Recommendations from national / regional decision making groups	
Stakeholder views	
CCG priorities	

Health economic considerations

Cost per year per patient

Abasaglar is available as cartridges of 100 units/ml for use in a reusable pen or as a pre-filled pen
100 units/ml. Both products cost £35.28 per pack of 5×3 ml (excluding VAT; price taken from MIMS, November 2015).

The cost of Abasaglar and other basal insulins will depend on the preparation chosen and the insulin dosage used. The list price of Abasaglar is about 15% lower than Lantus. The manufacturer estimates that the annual average cost of Abasaglar 100 units/ml once daily is £214.44 per person with type 1 diabetes and £278.77 per person with type 2 diabetes. This is based on estimated average daily doses of 25 units per day in type 1 diabetes and 40 units per day in type 2 diabetes.

Alternative treatments cost per patient per year

Insulin	5×3 ml cartridge	5×3 ml pre-filled pen
Insulatard NPH (isophane) insulin 100 units/ml solution	£22.90	£20.40
Humulin I NPH (isophane) insulin 100 units/ml solution	£19.08	£21.70
Insuman Basal NPH (isophane) insulin 100 units/ml solution	£17.50	£19.80
Lantus **insulin glargine 100 units/ml solution**	**£41.50**	**£41.50**
Abasaglar **biosimilar insulin glargine 100 units/ml solution**	**£35.28**	**£35.28**
Toujeo high-strength insulin glargine 300 units/ml	-	3×1.5 ml pre-filled pen, £33.13
Levemir insulin detemir 100 units/ml solution	£42.00	£42.00 or £44.85
Tresiba insulin degludec 100 units/ml solution	£72.00	£72.00
Tresiba insulin degludec 200 units/ml solution	-	3×3 ml pre-filled pen, £86.40
Costs are excluding VAT; taken from MIMS (November 2015).		

	Lantus®	Abasaglar®
5 x 3 mL (1500 units)*	£41.50 (3)	£35.28
Annual cost, (20 units) 100 patients	£20,197	£17,170
Annual cost (40 units) 100 patients	£40,393	£34,339
Annual cost (60 units) 100 patients	£60,590	£51,509

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